Aminolysis of Benzyl 2-Pyridyl Thionocarbonate and *t*-Butyl 2-Pyridyl Thionocarbonate: Effects of Nonleaving Groups on Reactivity and Reaction Mechanism

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A kinetic study is reported for nucleophilic substitution reactions of benzyl 2-pyridyl thionocarbonate (**5b**) and *t*-butyl 2-pyridyl thionocarbonate (**6b**) with a series of alicyclic secondary amines in H_2O at 25.0 ℃. General-base catalysis, which has often been reported to occur for aminolysis of esters possessing a C=S electrophilic center, is absent for the reactions of **5b** and **6b**. The Brønsted-type plots for the reactions of **5b** and **6b** are linear with $\beta_{nuc} = 0.29$ and 0.43, respectively, indicating that the reactions of **5b** proceed through a stepwise mechanism with formation of a zwitterionic tetrahedral intermediate ($T^\pm$) being the rate-determining step while those of **6b** proceed through a concerted mechanism. The reactivity of **5b** and **6b** is similar to that of their oxygen analogues (*i.e.*, benzyl 2-pyridyl carbonate **5a** and *t*-butyl 2-pyridyl carbonate **6a**, respectively), indicating that the effect of modification of the electrophilic center from C=O to C=S (*i.e.*, from **5a** to **5b** and from **6a** to **6b**) on reactivity is insignificant. In contrast, **6b** is much less reactive than **5b**, indicating that the replacement of the $PhCH_2$ in **5b** by the *t*-Bu in **6b** results in a significant decrease in reactivity as well as a change in the reaction mechanism (*i.e.*, from a stepwise mechanism to a concerted pathway). It has been concluded that the contrasting reactivity and reaction mechanism for the reactions of **5b** and **6b** are not due to the electronic effects of $PhCH_2$ and *t*-Bu but are caused by the large steric hindrance exerted by the bulky *t*-Bu in **6b**.

Key Words : Aminolysis, Electrophilic center, Nucleofugality, Intramolecular H-bonding interaction, Steric hindrance

Introduction

Numerous studies have been performed for nucleophilic displacement reactions of esters with amines due to their importance in biological processes as well as in synthetic applications.[1-10] Aminolysis of esters has been reported to proceed either through a concerted mechanism or through a stepwise pathway with one or two intermediates as shown in Scheme 1.[1-10] Many factors have been suggested to govern the reaction mechanisms (*e.g.*, the nature of reaction medium, the electrophilic center, the nonleaving group and the leaving group, etc.).[1-10]

The reactions of 4-nitrophenyl benzoate (**1a**) with a series
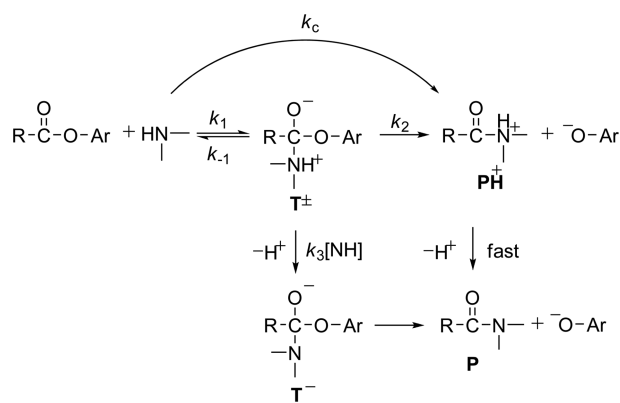
Scheme 1

of alicyclic secondary amines in H_2O have been reported to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate ($T^\pm$) on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.81$.[7a] In contrast, the corresponding reactions in MeCN have been suggested to proceed through a concerted mechanism based on a linear Brønsted-type plot with $\beta_{nuc} = 0.40$,[7d] indicating that the nature of the reaction medium governs the reaction mechanism. It has also been reported that the reactions of *O*-4-nitrophenyl thionobenzoate (**1b**) with the same alicyclic secondary amines proceed through two intermediates, $T^\pm$ and its deprotonated form T^- both in H_2O and MeCN, implying that the effect of changing the electrophilic center from C=O to C=S on reaction mechanism is significant.[8] A similar result has been reported for the corresponding reactions of 4-nitrophenyl phenyl carbonate (**2a**) and thionocarbonate (**2b**), *i.e.*, aminolysis of **2a** proceeds through a stepwise mechanism with $T^\pm$ as an intermediate, while the corresponding reaction of **2b** proceeds through two intermediates (*i.e.*, $T^\pm$ and T^-).[9]


X = O(**1a**), S(**1b**)   X = O(**2a**), S(**2b**)
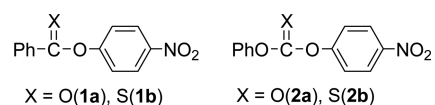
Interestingly, we have found that reactions of benzyl 4-pyridyl carbonate (**3**) with a series of alicyclic secondary amines proceed through $T^\pm$ and T^- in both H_2O and MeCN[10a,b] while the corresponding reactions of *t*-butyl 4-pyridyl carbonate (**4**) proceed through a concerted mechanism.[10c] This indicates
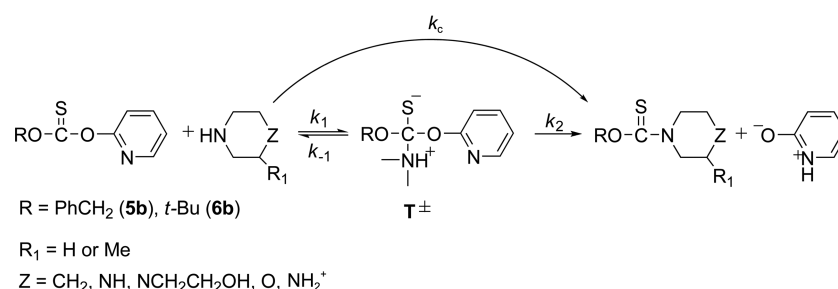
Scheme 2

that the replacement of the $PhCH_2$ group in **3** by the *t*-Bu group in **4** also controls the reaction mechanism.
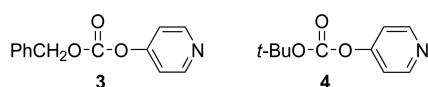
In contrast, the aminolyses of benzyl 2-pyridyl carbonate (**5a**) and *t*-butyl 2-pyridyl carbonate (**6a**) have been concluded to proceed through a forced concerted mechanism on the basis of the fact that the Brønsted-type plots are linear with $\beta_{nuc} = 0.49$ and 0.44 for the reactions of **5a** and **6a**, respectively.[10d] This implies that modification of the leaving group from 4-pyridyloxide to 2-pyridyloxide also cause a change in the reaction mechanism.
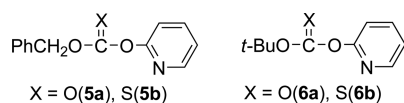
Our study has now been extended to reactions of benzyl 2-pyridyl thionocarbonate (**5b**) and *t*-butyl 2-pyridyl thionocarbonate (**6b**) with a series of alicyclic secondary amines in H_2O to investigate the effect of replacement of the $PhCH_2$ group in **5b** by the *t*-Bu group in **6b** on reactivity and reaction mechanism (Scheme 2). We have also investigated the effect of modification of the electrophilic center from C=O to C=S on reactivity and reaction mechanism by comparing the current kinetic results with those reported recently for the corresponding reactions of **5a** and **6a**.[10d]

Results and Discussion

The reactions were followed spectrophotometrically by monitoring the appearance of 2-hydroxypyridine under pseudo-first-order conditions (*e.g.*, the concentration of amines was kept in excess over that of substrates). All reactions obeyed first-order kinetics and the pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} *vs.* amine concentration were linear with excellent correlation coefficients (*e.g.*, $R^2 \geq 0.9995$) and passed through the origin, indicating that a general base catalysis by a second amine molecule is absent and the contribution of H_2O and/or OH^- from hydrolysis of amines to k_{obsd} is negligible. Accordingly, the second-order rate constants (k_N) for the aminolyses of

Table 1. Summary of second-order rate constants (k_N) for the reactions of benzyl 2-pyridyl carbonate **5a** and thionocarbonate **5b** with alicyclic secondary amines in H_2O at $25.0 \pm 0.1 \ ^\circ C^a$

	Amines	pK_a	k_N/M^{-1}s^{-1}	
			5a	**5b**
1	Piperidine	11.22	37.9	19.2
2	3-Methylpiperidine	11.07	44.0	26.8
3	Piperazine	9.82	19.1	18.7
4	1-(2-Hydroxyethyl)piperazine	9.38	5.03	6.07
5	Morpholine	8.36	3.07	5.33
6	Piperazinium Ion	5.68	0.110	0.643

*^{a}The k_N data for the reactions of **5a** were taken from ref. 10d.*

5b and **6b** were calculated from the slope of the linear plots and are summarized in Tables 1 and 2, respectively together with those reported previously for the corresponding reactions of benzyl 2-pyridyl carbonate (**5a**) and *t*-butyl 2-pyridyl carbonate (**6a**) to investigate the effect of modification of the electrophilic center from C=O to C=S on reactivity and reaction mechanism. The uncertainty in the k_N values is estimated to be less than $\pm 3\%$ from replicate runs.

Reactions of 5a and 5b. As shown in Table 1, the second-order rate constant k_N for the reactions of **5b** decreases as the amine basicity decreases, *e.g.*, it decreases from 19.2 M^{-1}s^{-1} to 6.07 and 0.643 M^{-1}s^{-1} as the pK_a of the conjugate acid of the amine decreases from 11.22 to 9.38 and 5.68, in turn. Interestingly, **5b** is less reactive than **5a** toward highly basic piperidine and 3-methylpiperidine but becomes more reactive toward the weakly basic amines.

To investigate the reaction mechanism, Brønsted-type plots have been constructed for the reactions of **5a** and **5b**. As shown in Figure 1, the Brønsted-type plots for the reactions of **5a** and **5b** are linear over 5 pK_a units when the k_N and pK_a values are statistically corrected using p and q (*i.e.*, $p = 2$ except $p = 4$ for piperazinium ion and $p = 1$ except $p = 2$ for piperazine).[11] It is also noted that the slope of the Brønsted-type plots is much smaller for the reactions of **5b** than for those of **5a** (*i.e.*, $\beta_{nuc} = 0.49$ and 0.29 for the reactions of **5a** and **5b**, respectively).

Since a β_{nuc} value of 0.5 ± 0.1 is typical for reactions reported previously to proceed through a concerted mechanism,[1-10] the reactions of **5a** were concluded to proceed through a concerted mechanism.[10d] On the other hand, the β_{nuc} value for aminolyses of esters which proceed through a
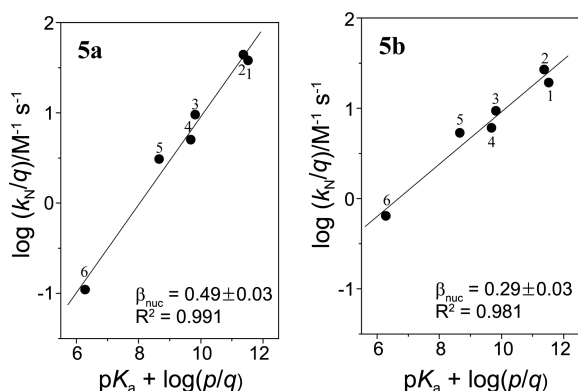
Figure 1. Brønsted-type plots for the reactions of **5a** and **5b** with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C. The identity of numbers is given in Table 1.

stepwise mechanism is known to be dependent on the rate-determining step (RDS), *e.g.*, β_{nuc} decreases from 0.8 ± 0.1 to 0.2-0.3 as the RDS changes from breakdown of the zwitterionic tetrahedral intermediate ($T^{\pm}$) to its formation.[1-10] Thus, one can propose that the aminolysis of **5b** proceeds through a stepwise mechanism in which formation of $T^{\pm}$ is the RDS on the basis of the β_{nuc} value of 0.29. It is apparent that modification of the electrophilic center from the C=O in **5a** to the C=S in **5b** is the cause of the change in the reaction mechanism (*i.e.*, from a concerted mechanism to a stepwise pathway).

It was expected that the reaction of **5a** would proceed through a stepwise mechanism with an intermediate as modeled by **I**, since it could be stabilized through the intramolecular H-bonding interaction.[10d] However, we have suggested that such intramolecular H-bonding interaction could accelerate the rate of leaving-group expulsion since the nucleofugality of the leaving group increases significantly upon the proton transfer from the aminium moiety of **I** to the leaving group.[10d] Furthermore, the "push" provided by the RO moiety of **I** through resonance interactions would also facilitate expulsion of the leaving group. Thus, the enhanced nucleofugality of the leaving group through the H-bonding interaction together the "push" provided by the RO group has been suggested to force the reactions of **5a** to proceed through a concerted mechanism.[10d]
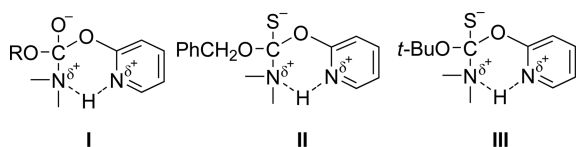
It is well known that C=S bond is not as strong as C=O bond due to inefficient orbital overlap and/or due to the ability of sulfur to stabilize a negative charge by distributing the electron cloud through its 3d orbitals. Castro *et al.* have reported that the ability of $C-S^-$ to form C=S is less favorable than that of $C-O^-$ to form C=O.[12] Besides, they found that expulsion of the leaving group from the $T^{\pm}$ is much slower for aminolysis of ethyl 4-nitrophenyl thionocarbonate than for the corresponding reaction of ethyl 4-nitrophenyl
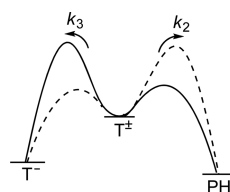

Figure 2. Qualitative comparative energy profile for the process from $T^{\pm}$ to T^- and PH^+.

carbonate.[12] Thus, one can expect that the $T^{\pm}$ formed from the reactions of **5b** (*i.e.*, **II**) would be less unstable than that formed from the corresponding reactions of **5a** (*i.e.*, **I**). This idea is consistent with the above argument that the aminolysis of **5b** proceeds through a stepwise mechanism, in which formation of a zwitterionic tetrahedral intermediate is the RDS.

Aminolyses of thiono esters (*e.g.*, **1b** and **2b**) have often been reported to proceed through a deprotonation process from $T^{\pm}$ to yield T^- by a second amine molecule (*i.e.*, the k_3 process in Scheme 1).[8,9,12] However, as mentioned in the result section, such deprotonation process is absent in the current aminolysis of **5b** and **6b** since the plots of k_{obsd} *vs.* [amine] are linear. Thus, one can suggest that the enhanced nucleofugality of the leaving group through the intramolecular H-bonding interaction as illustrated in **II** is responsible for the absence of the deprotonation process.

To account for the above argument, a qualitative energy diagram for aminolysis of esters has been illustrated in Figure 2. One might expect that the reaction would proceed through the deprotonation process when the energy barrier to form T^- from $T^{\pm}$ is lower than that to form PH^+ (*i.e.*, the k_3 path through the dotted line). On the contrary, the reaction would proceed without the deprotonation process when the energy barrier to form PH^+ from $T^{\pm}$ is lower than that to form T^- (*i.e.*, the k_2 path through the solid line).

It has been suggested that k_3 is independent of the amine basicity.[8,9] This is because a more basic amine would deprotonate more rapidly from the aminium moiety of $T^{\pm}$ while the aminium ion would hold the proton more strongly as the amine becomes more basic. Thus, the amine basicity could not influence the energy barrier to form T^- from $T^{\pm}$. In contrast, the energy barrier to form PH^+ from $T^{\pm}$ is strongly dependent on the nucleofugality of the leaving group. As mentioned above, the current aminolysis of **5b** is expected to proceed through **II**, in which the intramolecular H-bonding interaction increases the rate of leaving-group expulsion (*i.e.*, an increase in the k_2 value). This is because the leaving group from **II** is the zwitterionic form of 2-hydroxypyridine, which is a weak base since the pK_a of the conjugate acid of 2-hydroxypyridine is reported to be 0.75.[13] Accordingly, one can suggest that the intramolecular H-bonding interaction in **II** leads the reaction to proceed through the k_2 path by decreasing the leaving-group basicity.

Reactions of 6a and 6b. As shown in Table 2, the k_N value for the reactions of **6b** decreases as the amine basicity decreases. Interestingly, the k_N values for the reactions of **6a** and **6b** are similar, indicating that the effect of modification

Table 2. Summary of second-order rate constants (k_N) for the reactions of *t*-butyl 2-pyridyl carbonate **6a** and thionocarbonate **6b** with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C[a]

	Amines	pK_a	k_N/M^{-1}s^{-1}	
			6a	**6b**
1	Piperidine	11.22	0.735	0.757
2	3-Methylpiperidine	11.07	0.748	0.721
3	Piperazine	9.82	0.443	0.482
4	1-(2-Hydroxyethyl)piperazine	9.38	0.119	0.117
5	Morpholine	8.36	0.0828	0.0879
6	Piperazinium ion	5.68	0.00387	0.00373

[a]The k_N data for the reactions of **6a** were taken from ref. 10d.

of the electrophilic center from C=O to C=S on reactivity is negligible. However, comparison of the reactivity of **5b** and **6b** reveals that the latter is much less reactive than the former, implying that the effect of modification of the non-leaving group from benzyloxycarbonyl to *t*-butoxycarbonyl (*i.e.*, **5b** → **6b**) on reactivity is significant.

The effect of amine basicity on k_N has been illustrated in Figure 3. The statistically corrected Brønsted-type plots for the reactions of **6a** and **6b** are linear. It is also noted that β_{nuc} for the reactions of **6b** is practically identical to that for the reactions of **6a** ($\beta_{nuc} = 0.44$), indicating that the reactions of both **6a** and **6b** proceed through the same mechanism (*i.e.*, a concerted mechanism). However, the β_{nuc} value for the reactions of **6b** is much larger than the β_{nuc} of 0.29 for the corresponding reactions of **5b** (Figure 1), which has been concluded in the preceding section to proceed through a stepwise mechanism with formation of T$^\pm$ being the RDS. Thus, one can suggest that modification of the electrophilic center from C=O to C=S (*i.e.*, **6a** → **6b**) does not influence the reaction mechanism, but replacement of the PhCH$_2$ group in **5b** by the *t*-Bu group in **6b** results in a change in the reaction mechanism.

The electronic effect of PhCH$_2$ and *t*-Bu is similar since σ_I = 0.03 and −0.03 for PhCH$_2$ and *t*-Bu, respectively.[14] Thus, the electronic effects of the nonleaving groups of **5b** and **6b** are not responsible for the contrasting reaction mechanism found in this study. It is apparent that the bulky *t*-Bu in **6b**
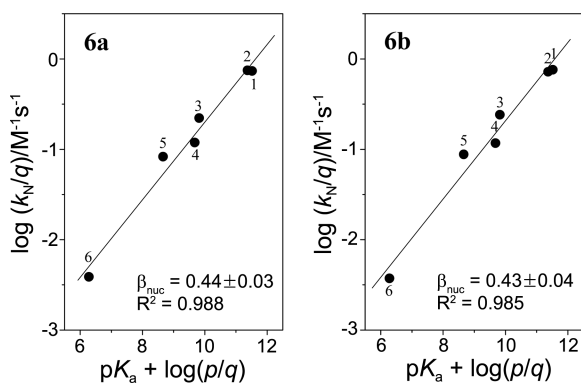
would exert significantly stronger steric hindrance than the PhCH$_2$ in **5b** since the steric constant $E_s = -0.38$ for PhCH$_2$ and $E_s = -1.54$ for *t*-Bu.[14] This idea can be further supported by the fact that **6b** is significantly less reactive than **5b**.

One might attribute the contrasting reaction mechanisms for the reactions of **5b** and **6b** to the steric hindrance. It is apparent that steric hindrance would be more significant as the hybridization of the reaction center changes from sp^2 to sp^3. Thus, the steric hindrance exerted by the *t*-Bu group in **6b** would become even stronger upon formation of the zwitterionic tetrahedral intermediate T$^\pm$ (*i.e.*, **III**). Since such steric hindrance would be diminished by expelling the leaving group from the T$^\pm$, the bulky *t*-Bu group in **III** would favor to expel the leaving group to reduce the steric hindrance (*i.e.*, an increase in k_2). Accordingly, one might expect that the T$^\pm$ for the reactions of **6b** (*i.e.*, **III**) is significantly more unstable than the T$^\pm$ for the corresponding reactions of **5b** (*i.e.*, **II**) and the enhanced instability of T$^\pm$ forces the reactions of **6b** to proceed through a concerted mechanism.

Conclusions

The current study has allowed us to conclude the following: (1) The reactions of **5b** and **6b** proceed without general base catalysis. Enhanced nucleofugality of the leaving group through the intramolecular H-bonding interaction as modeled by **II** and **III** is responsible for the absence of the deprotonation process from T$^\pm$. (2) The effect of modification of the electrophilic center from C=O to C=S (*e.g.*, from **5a** to **5b** and from **6a** to **6b**) on reactivity is insignificant. (3) The replacement of the PhCH$_2$ in **5b** by *t*-Bu in **6b** results in a significant decrease in reactivity. Large steric hindrance exerted by the bulky *t*-Bu in **6b** is responsible for its decreased reactivity. (4) The Brønsted-type plots for the reactions of **5b** and **6b** are linear with $\beta_{nuc} = 0.29$ and 0.43, respectively, indicating that the reactions of **5b** proceed through a stepwise mechanism with formation of T$^\pm$ (*i.e.*, **II**) being the RDS while those of **6b** proceed through a concerted mechanism. (5) Large steric hindrance exerted by the bulky *t*-Bu in **6b** makes **III** highly unstable and forces the reactions to proceed through a concerted mechanism.

Experimental Section

Materials. Substrates **5b** and **6b** were prepared through the reaction of di-2-pyridyl thionocarbonate (DPT)[15] with benzyloxymagnesium bromide, which was generated from the reaction of benzyl alcohol and ethylmagnesium bromide, and potassium *t*-butoxide, respectively, in THF. The crude products were purified by short pathway silica gel (Davisil, pH = 7) column chromatography or recrystallization. Their purity was checked by their melting point, ^{1}H and ^{13}C NMR spectra (Supporting Information). Amines and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. Kinetic study was performed using a UV-Vis

Figure 3. Brønsted-type plots for the reactions of **6a** and **6b** with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C. The identity of numbers is given in Table 2.

spectrophotometer equipped with a constant-temperature circulating bath. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was kept at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.01 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of H_2O and the amine nucleophile. The amine stock solution of *ca.* 0.2 M was prepared in a 25.0 mL volumetric flask by adding 2 equiv. of amine and 1 equiv. of HCl solution to make a self-buffered solution. Reactions were followed generally for 9 half-lives and k_{obsd} were calculated using the equation, $\ln (A_\infty - A_t)$ *vs. t*.

Supporting Information. ^{1}H and ^{13}C NMR spectra of compounds **5b** and **6b**.

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