

Alkali-Metal Ion Catalysis in Alkaline Ethanolysis of 2-Pyridyl Benzoate and Benzyl 2-Pyridyl Carbonate: Effect of Modification of Nonleaving Group from Benzoyl to Benzyloxycarbonyl

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A kinetic study is reported on nucleophilic displacement reactions of benzyl 2-pyridyl carbonate **6** with alkali-metal ethoxides, EtOM (M = Li, Na, and K), in anhydrous ethanol at 25.0 ± 0.1 °C. The plots of pseudo-first-order rate constant k_{obsd} vs. [EtOM] curve upward, a typical phenomenon reported previously for alkaline ethanolysis of esters in which alkali-metal ions behave as a Lewis-acid catalyst. The k_{obsd} value for the reaction of **6** with a fixed EtOK concentration decreases rapidly upon addition of 18-crown-6-ether (18C6), a complexing agent for K^+ ion up to $[18\text{C6}]/[\text{EtOK}] = 1.0$ and then remains constant thereafter, indicating that the catalytic effect exerted by K^+ ion disappears in the presence of excess 18C6. The reactivity of EtOM towards **6** increases in the order $\text{EtO}^- < \text{EtOLi} < \text{EtONa} < \text{EtOK}$, which is contrasting to the reactivity order reported for the corresponding reactions of 2-pyridyl benzoate **4**, *i.e.*, $\text{EtO}^- < \text{EtOK} < \text{EtONa} < \text{EtOLi}$. Besides, **6** is 1.7 and 3.5 times more reactive than **4** towards dissociated EtO^- and ion-paired EtOK, respectively. The reactivity difference and the contrasting metal-ion selectivity are discussed in terms of electronic effects and transition-state structures.

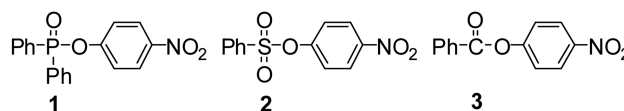
Key Words : Metal ion catalysis, Ethanolysis, Electrophilicity, Nucleofugality, Transition state

Introduction

Nucleophilic substitution reactions of esters have intensively been investigated due to their importance in biological processes as well as synthetic applications.¹⁻¹⁴ Reactions of esters with amines have been reported to proceed through a stepwise mechanism in which the rate-determining step (RDS) is dependent on the basicity of the incoming amine and the leaving group.¹⁻⁹ On the other hand, reactions of esters with anionic nucleophiles (*e.g.*, OH^- , RO^- , ArO^-) have been suggested to proceed through a concerted mechanism or through a stepwise pathway depending on reaction conditions (*e.g.*, the nature of solvents, nucleophiles and electrophilic centers).¹⁰⁻¹⁴

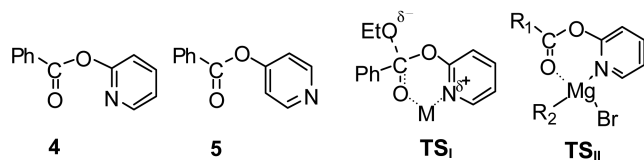
Metal ions, as a Lewis-acid catalyst, are known to increase rates of nucleophilic substitution reactions of various esters by increasing the electrophilicity or nucleofugality through coordination with the electrophilic center or the leaving group, respectively.¹⁵⁻²¹ Since Lewis acidity increases with increasing the charge density of metal ions, most studies have focused on multivalent metal ions (*e.g.*, Mg^{2+} , Mn^{2+} , Zn^{2+} , La^{3+} , Eu^{3+} , Co^{3+}).¹⁶ Although alkali-metal ions are ubiquitous in nature and are known to play important roles in biological processes (*e.g.*, a Na^+ pump which functions to keep high K^+ and low Na^+ concentration in mammalian cells), the effect of alkali metal ions has much less been investigated.¹⁷⁻²¹ The first systematic study on the effect of alkali-metal ions was performed by Buncler and his co-workers for nucleophilic substitution reactions of 4-nitro-

phenyl diphenylphosphinate **1** with alkali-metal ethoxides (EtOM, M = Li, Na, K) in anhydrous ethanol.¹⁷ They found that alkali metal ions catalyze the reactions and the catalytic effect increases as the size of the metal ion decreases, *i.e.*, $\text{K}^+ < \text{Na}^+ < \text{Li}^+$.¹⁷ A contrasting reactivity pattern has been reported for the corresponding reactions of 4-nitrophenyl benzenesulfonate **2**, *i.e.*, the catalytic effect increases as the size of M^+ ions increases (*i.e.*, $\text{Li}^+ < \text{Na}^+ < \text{K}^+$).¹⁸ The effect of M^+ ions on reactions of 4-nitrophenyl benzoate **3** was also investigated.^{20,21} However, M^+ ion effect on reactivity of **3** has been reported to be insignificant, indicating that the role of alkali metal ion is dependent on the nature of the electrophilic center (*e.g.*, $\text{P}=\text{O}$, SO_2 or $\text{C}=\text{O}$).

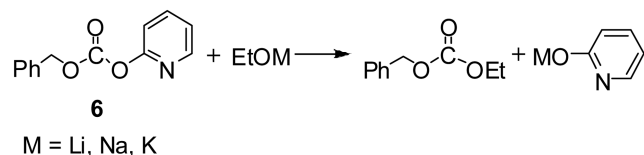


We have recently shown that alkali-metal ions exhibit a large catalytic effect in the nucleophilic substitution reaction of 2-pyridyl benzoate **4** with EtOM in anhydrous ethanol, while the catalytic effect becomes negligible for the corresponding reactions of 4-pyridyl benzoate **5**, an isomer of **4**.²¹ Accordingly, the large catalytic effect shown by M^+ ions has been attributed to stabilization of the transition state (TS) through formation of a six-membered cyclic TS (*e.g.*, TS₁), since such a cyclic TS structure is not possible for the reactions of **5**.²¹ This idea is consistent with the report that esters possessing a 2-pyridyl moiety behaves as an excellent

acylating agent in reactions with Grignard reagents as well as in those with cupric bromide or lithium dialkylcuprate through a 6-membered cyclic complex (e.g., TS_{II}), in which metal ion acts as a strong Lewis acid catalyst.^{22,23}



Our study has now been extended to the nucleophilic substitution reactions of benzyl 2-pyridyl carbonate **6** with EtOM (M = Li, Na, K) in anhydrous ethanol (Scheme 1). The kinetic data for the current reactions of **6** have been compared with those reported recently for the corresponding reactions of **4** to investigate the effect of modification of the nonleaving group from benzoyl to benzyloxycarbonyl on the reactivity and the role of M⁺ ions.



Scheme 1

Results and Discussion

The reactions were monitored spectrophotometrically by following the appearance of the leaving 2-pyridyloxide at 297nm under pseudo-first-order conditions with large excess EtOM. All reactions in the current study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the slope of the linear plots of $\ln(A - A_t)$ vs. t . The correlation coefficients of the linear plots are higher than 0.9995. From replicate runs, the uncertainty in the k_{obsd} values is estimated to be less than $\pm 3\%$. The k_{obsd} values and detailed kinetic conditions for the reactions of **6** with EtOM are summarized in Tables S1-S5 in the Supporting Information.

Effect of Alkali Metal Ions on Reactivity. As shown in Figure 1(a), the plots of k_{obsd} vs. [EtOM] for reactions of **6** with EtOM curve upward while the corresponding plot for the reaction with EtOK in the presence of 18-crown-6-ether (18C6), a complexing agent for K⁺ ion, is linear with significant decreased k_{obsd} values. It is apparent from the upward curvature that the alkali-metal ions catalyze the reactions of **6**, while the linear plot for the reaction with EtOK/18C6 indicates that the catalytic effect shown by K⁺ ion disappears in the presence of the complexing agent.

The curved plots for the reactions of **6** are similar to those reported recently for the corresponding reactions of **4** as demonstrated in Figure 1(b).^{21a} However, the reactivity order of EtOM for the reactions of **6** is contrasting to that reported for the reactions of **4**, i.e., EtOK > EtONa > EtOLi for the

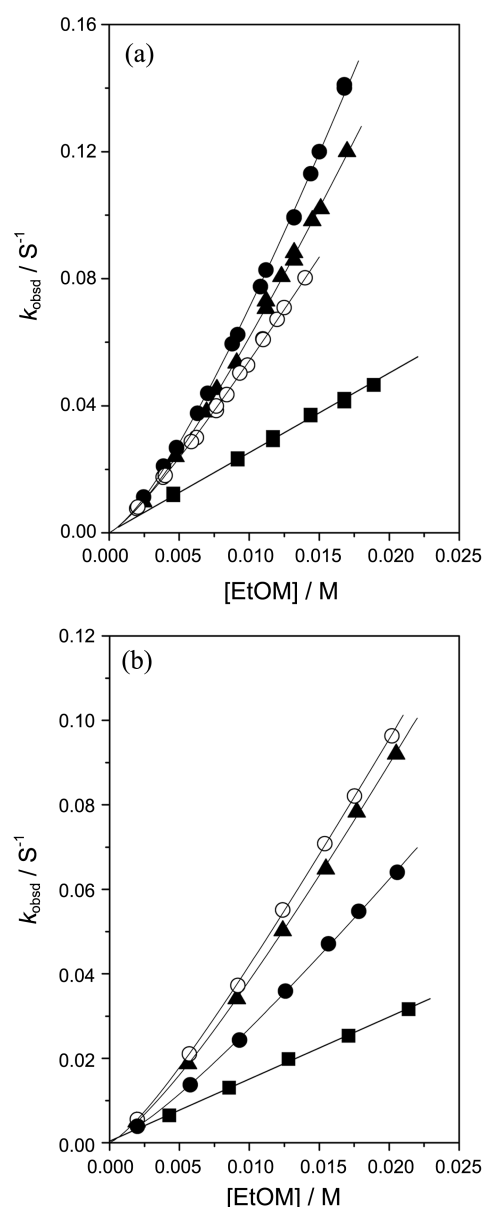


Figure 1. Plots of k_{obsd} vs. [EtOM] for the reactions of benzyl 2-pyridyl carbonate **6** (a) and 2-pyridyl benzoate **4** (b) with EtOK (●), EtONa (▲), EtOLi (○) and EtOK/18C6 (■) ([18C6]/[EtOK] = 2.0) in anhydrous EtOH at 25.0 ± 0.1 °C. The kinetic data for the reaction of **4** were taken from ref. 21a.

reactions of **6** while EtOK < EtONa < EtOLi for those of **4**.²¹

To examine the validity of the above argument that M⁺ ions behave as a Lewis-acid catalyst, the reaction of **6** with EtOK has been performed at a fixed EtOK concentration with varying the concentration of 18C6, i.e., [EtOK] = 15.0 mM and the [18C6]/[EtOK] = 0, 0.35, 0.53, 0.71, 1.00, 2.10, 3.00, 4.24, and 5.30. As shown in Figure 2, the k_{obsd} value decreases rapidly upon addition of the complexing agent up to [18C6]/[EtOK] = 1.0 and then remains nearly constant thereafter. This supports clearly the preceding argument that K⁺ ion catalyzes the reaction of **6** and the catalytic effect disappears completely when [18C6]/[EtOK] ≥ 1.0 .

Dissection of k_{obsd} into k_{EtOM} and k_{EtO^-} . To quantify the

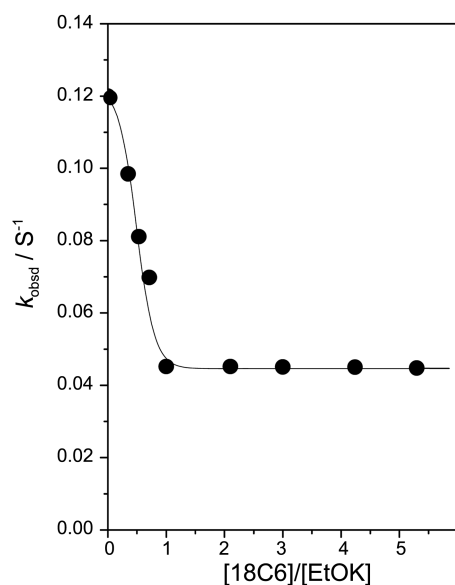
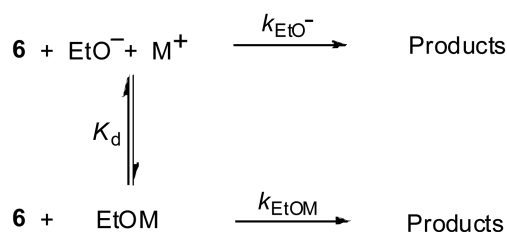


Figure 2. Plot showing effect of added 18C6 on the reactivity of EtOK toward benzyl 2-pyridyl carbonate **6** in anhydrous EtOH at $25.0 \pm 0.1^\circ\text{C}$. ($[\mathbf{6}] = 5.19 \times 10^{-2} \text{ mM}$, $[\text{EtOK}] = 15.0 \text{ mM}$).



Scheme 2

catalytic effect exerted by M^+ ions, k_{obsd} has been dissected into k_{EtO^-} and k_{EtOM} , the second-order rate constant for the reaction with the dissociated EtO^- and ion-paired EtOM, respectively. In anhydrous ethanol, EtOM was reported previously to exist as dissociated EtO^- and ion-paired EtOM when $[\text{EtOM}] < 0.1 \text{ M}$.²⁴ The concentration of EtOM in this study is much lower than 0.1 M. Accordingly, one might expect that substrate **6** would react with the dissociated EtO^- and ion-paired EtOM as shown in Scheme 2.

On the basis of the reactions proposed in Scheme 2, Eq. (1) can be derived. Under a pseudo-first-order kinetic condition, k_{obsd} can be expressed as Eq. (2). It is evident that the dissociation constant $K_d = [\text{EtO}^-]_{\text{eq}}[\text{M}^+]_{\text{eq}}/[\text{EtOM}]_{\text{eq}}$, and $[\text{EtO}^-]_{\text{eq}} = [\text{M}^+]_{\text{eq}}$ at equilibrium. Thus, Eq. (2) becomes eq (3). The concentrations of $[\text{EtO}^-]_{\text{eq}}$ and $[\text{EtOM}]_{\text{eq}}$ can be calculated from the reported K_d value and the initial concentration of EtOM (*i.e.*, $[\text{EtOM}]_0$) using Eqs. (4) and (5).

$$\text{Rate} = k_{\text{EtO}^-}[\text{EtO}^-]_{\text{eq}}[\mathbf{6}] + k_{\text{EtOM}}[\text{EtOM}]_{\text{eq}}[\mathbf{6}] \quad (1)$$

$$k_{\text{obsd}} = k_{\text{EtO}^-}[\text{EtO}^-]_{\text{eq}} + k_{\text{EtOM}}[\text{EtOM}]_{\text{eq}} \quad (2)$$

$$k_{\text{obsd}}/[\text{EtO}^-]_{\text{eq}} = k_{\text{EtO}^-} + k_{\text{EtOM}}[\text{EtO}^-]_{\text{eq}}/K_d \quad (3)$$

$$[\text{EtOM}]_0 = [\text{EtO}^-]_{\text{eq}} + [\text{EtOM}]_{\text{eq}} \quad (4)$$

$$[\text{EtO}^-]_{\text{eq}} = [-K_d + (K_d^2 + 4K_d[\text{EtOM}]_0)^{1/2}]/2 \quad (5)$$

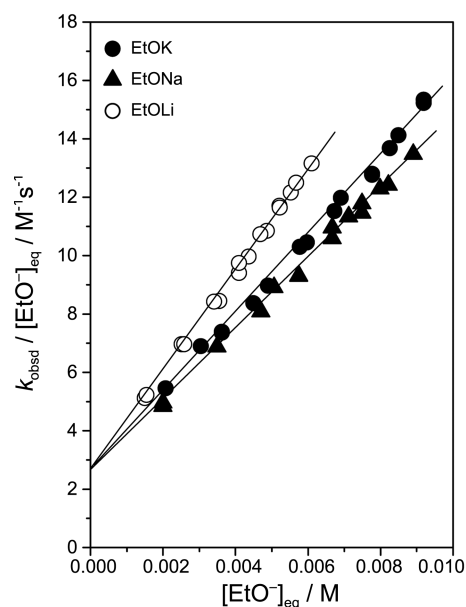


Figure 3. Plots illustrating dissection of k_{obsd} into the second-order rate constants k_{EtO^-} and k_{EtOM} for the reactions of benzyl 2-pyridyl carbonate **6** with EtOK (●), EtONa (▲), and EtOLi (○) in anhydrous EtOH at $25.0 \pm 0.1^\circ\text{C}$.

One might expect that the plot of $k_{\text{obsd}}/[\text{EtO}^-]_{\text{eq}}$ vs. $[\text{EtO}^-]_{\text{eq}}$ is linear with a positive intercept, if the reaction proceeds as suggested in Scheme 2. In fact, the plots shown in Figure 3 for the reaction of **6** with EtOM are linear with a common intercept, indicating that the above equations derived from the reactions in Scheme 2 are correct. Thus, one can calculate the k_{EtO^-} and k_{EtOM}/K_d values from the intercept and the slope of the linear plots, respectively. The k_{EtOM} value can be calculated from the k_{EtOM}/K_d ratios determined above and the K_d value reported previously (*i.e.*, $K_d = 4.72 \times 10^3$, 9.80×10^3 , and $1.11 \times 10^2 \text{ M}$ for EtOLi, EtONa, and EtOK, in turn).²⁵ The calculated k_{EtO^-} and k_{EtOM} values in this way are summarized in Table 1 together with those reported recently for the corresponding reactions of **4** for comparison.

As shown in Table 1, the reactivity of EtOM toward substrate **6** increases as the size of M^+ ion increases, *i.e.*, $\text{EtOLi} < \text{EtONa} < \text{EtOK}$. The reactivity order found for the current reactions of **6** is contrasting to that reported for the corresponding reactions of **4**, *i.e.*, $\text{EtOK} < \text{EtOLi} < \text{EtONa}$.^{21a} Furthermore, the carbonate **6** is *ca.* 1.7 and 3.1

Table 1. Summary of second-order rate constants from ion-pairing treatment of kinetic data for the reactions of 2-pyridyl benzoate **4** and benzyl 2-pyridyl carbonate **6** with EtOM in anhydrous EtOH at $25.0 \pm 0.1^\circ\text{C}$

EtOM	4		6	
	$k_{\text{EtOM}}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtOM}}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{EtO}^-}/\text{M}^{-1}\text{s}^{-1}$
EtOLi	6.48	1.46	8.24	2.43
EtONa	7.19	1.74	12.0	2.49
EtOK	4.90	1.45	15.2	2.44
EtOK/18C6	-	1.46	-	2.44

^aThe kinetic data for the reaction of **4** were taken from ref. 21a.

times more reactive than **4** towards the dissociated EtO^- and ion-paired EtOK , respectively. Thus, the current study shows that modification of the nonleaving-group from benzoyl to benzyloxycarbonyl (*i.e.*, from **4** to **6**) results in an increase in reactivity and a contrasting metal-ion selectivity.

Origin of Enhanced Reactivity and Contrasting M^+ ion Effects. As shown in Table 1 and Figure 1, **6** is more reactive than **4** toward the dissociated EtO^- and ion-paired EtOM . It is well known that the rate of nucleophilic substitution reactions is governed by many factors (*e.g.*, reaction mechanism, solvent, basicity of nucleophile and leaving group, resonance and inductive effects, *etc.*). One might expect that modification of the nonleaving-group from benzoyl to benzyloxycarbonyl would not affect the reaction mechanism. Besides, factors such as solvent, nucleophile and leaving-group basicity cannot be responsible for the fact that **6** is more reactive than **4**. This is because the solvent, nucleophile, and leaving group are the same for both reactions of **4** and **6** (*i.e.*, anhydrous ethanol as the solvent while ethoxide and 2-pyridyloxide ion as the nucleophile and leaving group, respectively). Thus, one might suggest that other factors (*e.g.*, inductive and/or resonance effects) are responsible for the difference in reactivity of **4** and **6**.

PhO is a stronger electron-withdrawing group than Ph on the basis of their σ_1 values (*e.g.*, $\sigma_1 = 0.38$ for PhO and 0.10 for Ph), while the former is also a stronger electron-donating group than the latter on the basis of their σ_R values (*e.g.*, $\sigma_R = -0.34$ for PhO and -0.11 for Ph). The σ_1 and σ_R values for PhCH_2O are not available but are expected to be similar to those of PhO . Thus, the fact that **6** is more reactive than **4** suggests that the inductive effect is more important than the resonance effect for the reactions of **4** and **6**.

One can propose another possibility that might account for the difference in reactivity and the contrasting M^+ ion selectivity for the reactions of **4** and **6**. As mentioned above from Figure 1 and Table 1, the M^+ ion selectivity for the reaction of **6** with EtOM is quite different from that reported for the corresponding reaction of **4**. It has been reported that M^+ ion catalyzes the reaction of **4** with EtOM through a 6-membered cyclic TS structure (*i.e.*, TS_I), in which the M^+ ion increases the electrophilicity of the reaction center and/or the nucleofugality of the leaving group. On the other hand, one might suggest two different TS structures for the reaction of **6** with EtOM as modeled by TS_{III} and TS_{IV} . Note that TS_{III} for the reaction of **6** is similar to TS_I proposed for the corresponding reaction of **4**, while TS_{IV} is not possible for the reaction of **4**. Thus, one might expect that M^+ ion selectivity would be the same for both reactions of **4** and **6**, if the reaction of **6** proceeds through TS_{III} . However, as mentioned above, M^+ ion selectivity for the current reaction of **6**

contrasts to that reported for the reaction of **4**. Thus, one cannot exclude a possibility that the reaction of **6** with EtOM would proceed through TS_{IV} , in which M^+ ion catalyzes the reaction by increasing the electrophilicity and/or nucleofugality.

Conclusions

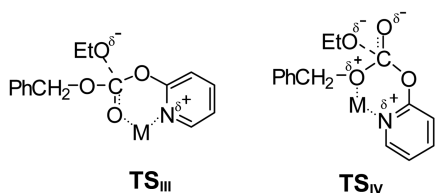
The current study has allowed us to conclude the following: (1) The plot of k_{obsd} vs. $[\text{EtOM}]$ curves upward, implying that M^+ ions catalyze the reaction of **6**. (2) The k_{obsd} value for the reaction with EtOK decreases rapidly upon addition of 18C6 up to $[\text{18C6}]/[\text{EtOK}] = 1.0$ and then remains nearly constant thereafter, indicating that the catalytic effect exerted by K^+ ion disappears in the presence of 18C6. (3) Dissection of k_{obsd} into k_{EtO^-} and k_{EtOM} reveals that the reactivity of EtOM towards **6** increases in the order $\text{EtO}^- < \text{EtOLi} < \text{EtONa} < \text{EtOK}$, which contrasts to that reported for the corresponding reaction of **4**, *i.e.*, $\text{EtO}^- < \text{EtOK} < \text{EtOLi} < \text{EtONa}$. (4) Substrate **6** is 1.7 and 3.5 times more reactive than **4** towards dissociated EtO^- and ion-paired EtOK , respectively. The inductive effect (σ_I) rather than resonance effect (σ_R) is responsible for the fact that **6** is more reactive than **4**. (5) TS_{IV} might be responsible for the M^+ ion selectivity observed for the reaction of **6**.

Experimental Section

Materials. Compound **6** was prepared readily from the reaction of 2-hydroxypyridine with benzyl chloroformate, which was generated from the reaction of phosgene and benzyl alcohol, in the presence of triethylamine in methylene chloride. The crude product was purified by recrystallization and its purity was checked by its melting point and ^1H and ^{13}C NMR spectra. The EtOM stock solutions were prepared by dissolving the respective alkali metal in anhydrous ethanol under N_2 and stored in the refrigerator. The concentration of EtOM was measured by titration with mono potassium phthalate. Crown ether (18C6) was recrystallized from acetonitrile and dried under vacuum. The anhydrous ethanol was further dried over magnesium and distilled under N_2 just before use.

Kinetics. Kinetic study was performed using a UV-vis spectrophotometer equipped with a constant-temperature circulating bath. The reactions were followed by monitoring the appearance of the leaving 2-pyridyloxide at 297 nm. Reactions were followed generally for 9-10 half-lives and k_{obsd} were calculated using the equation, $\ln(A_\infty - A_t)$ vs. t .

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Supporting Information. Tables S1-S5: The kinetic conditions and results for the reactions of **6** with EtOM.

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