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Elimination Reactions of (*E*)-2,4,6-Trinitrobenzaldehyde *O*-benzoyloximes Promoted by R_2NH in MeCN. Change of Reaction Mechanism

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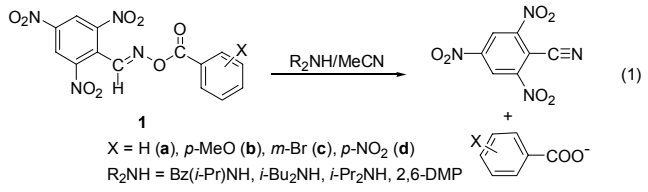
Nitrile-forming elimination reactions of (*E*)-benzaldoxime derivatives have been extensively investigated under various conditions.[1-7] The reactions proceeded by the E2 mechanism in MeCN despite the fact that the reactants have *syn* stereochemistry, poor leaving, and sp^2 hybridized β-carbon atom, all of which favor E1cb- or E1cb-like transition state.[8-11] Moreover, the transition state structures were relatively insensitive to the variation of the reactant structures. The results have been attributed to the poor anion solvating ability of MeCN, which favors E2 transition state with maximum charge dispersal. For eliminations from strongly activated (*E*)-2,4-$(NO_2)_2C_6H_3CH$=$NOC(O)C_6H_4X$, a change in the reaction mechanism from E2 to $(E1cb)_{irr}$ was observed as the base-solvent was changed from R_2NH in MeCN to $R_2NH/R_2NH_2^+$ in 70 mol % MeCN(aq).[7] A combination of a strong electron-withdrawing β-aryl group and anion-solvating protic solvent was required for the mechanistic change.

We were interested in learning if a change to the E1cB mechanism could be realized in aprotic solvent by making the β-aryl group even more electron-withdrawing. To explore such possibility, we have now studied the reactions of (*E*)-2,4,6-trinitrobenzaldehyde *O*-benzoyloxime with R_2NH in MeCN (eq 1). This substrate is the most strongly activated one studied so far in the (*E*)-benzaldehyde *O*-benzoyloxime series. By comparing with the existing data for eliminations from (*E*)-2,4-$(NO_2)_2C_6H_3CH$=$NOC(O)C_6H_4X$, the effect of β-aryl substituent was assessed.



1 (1)

X = H (**a**), *p*-MeO (**b**), *m*-Br (**c**), *p*-NO_2 (**d**)
R_2NH = Bz(*i*-Pr)NH, *i*-Bu_2NH, *i*-Pr_2NH, 2,6-DMP

Product studies. (*E*)-2,4,6-Trinitrobenzaldehyde *O*-benzoyloximes **1a-d** were prepared by reacting appropriate benzoyl chlorides with (*E*)-2,4,6-trinitrobenzaldoxime in aqueous NaOH solution as described previously.[1] The reaction of **1a** with *i*-Bu_2NH in MeCN produced 2,4,6-trinitrobenzonitrile in 93% yield. No trace of (*E*)-2,4,6-trinitrobenzaldehyde oxime could be detected by TLC.

Kinetic studies. The rates of elimination reaction were followed by monitoring the decrease in the absorption at the λ_{max} for the substrates in the range of 258 ~ 280 nm. Excellent pseudo-first order kinetics plots, which covered for at least three half-lives were obtained. The plots of k_{obs} versus base concentration for the reaction of **1a** were straight lines passing through the origin, indicating that the reactions are second-order, first order to the substrate and first order to the base (Figure S1, Supporting Information). Moreover, the k_2 value calculated from the slope of the plot was in excellent agreement (within ±3%) with the k_2 calculated by using a single data point. Therefore, the rate constants were determined at a single base concentration. The overall second-order rate constants k_2 were obtained by dividing the k_{obs} by the base concentration. Values of k_2 for eliminations from **1a-d** are summarized in Table 1. Except for the rate data determined with *i*-Pr_2NH, the k_2 value increased with basicity and the leaving group ability. The slower rate of eliminations from **1a**, **1c**, and **1d** with *i*-Pr_2NH than with *i*-Bu_2NH as the base can be attributed to the greater steric requirement of the former.

The k_2 values for eliminations from **1a-d** showed excellent correlations with the pK_a values of the promoting bases on the Brönsted plot, if the data for *i*-Pr_2NH was excluded (Figure 1). The negative deviation noted for *i*-Pr_2NH can be attributed to the steric effect. Therefore, the β values were calculated from the straight lines without the data for *i*-Pr_2NH. Similarly, the k_2 values correlated satisfactorily with the leaving group pK_{lg} values (Figure 2). The β and $|\beta_{lg}|$ values were in the range of 0.39 ~ 0.41 and 0.18 ~ 0.23, respectively. The β and $|\beta_{lg}|$ values remained nearly the same within experimental error regardless of the leaving group and the base strength variation (Tables 2 and 3).

Table 1. Second-order rate constants for nitrile-forming elimination reactions from (*E*)-2,4,6-$(NO_2)_3C_6H_2CH$=$NOC(O)C_6H_4X$[a] promoted by R_2NH in MeCN at 25.0 °C

R_2NH[b]	pK_a[e]	k_2, $M^{-1}s^{-1}$ [d,g]			
		X = H	X = *p*-OMe	X = *m*-Br	X = *p*-CF_3
Bz(*i*-Pr)NH	16.8	4.25	2.55	7.55	7.90
i-Bu_2NH	18.2	13.7	8.15	25.3	27.5
i-Pr_2NH	18.5	11.5	13.2	22.2	25.3
2,6-DMP[f]	18.9	17.4	30.8	51.3	57.3

[a][Substrate] = 8.0×10^{-5} M. [b][R_2NH] = 4.0×10^{-5} M. [c]Reference 11. [d]Estimated uncertainty, ± 3%. [e]Average of three or more rate constants. [f]*cis*-2,6-Dimethylpiperidine.

Table 2. Brønsted β values for elimination from (*E*)-2,4,6-$(NO_2)_3C_6H_2CH$=NOC(O)C_6H_4X (**1a-d**) promoted by R_2NH in MeCN at 25.0 °C

	X = *p*-OMe	X = H	X = *m*-Br	X = *p*-CF_3
pK_{lg}[a]	21.3	20.7	19.5	19.2[b]
β	0.39 ± 0.03	0.40 ± 0.03	0.39 ± 0.02	0.41 ± 0.02

[a]Reference 12. [b]Determined from the slope of the plot of σ *vs* pK_a.

Table 3. Brønsted β_{lg} values for elimination from (*E*)-2,4,6-$(NO_2)_3C_6H_2CH$=NOC(O)C_6H_4X promoted by R_2NH in MeCN at 25.0 °C

R_2NH	Bz(*i*-Pr)NH	*i*-Bu_2NH	*i*-Pr_2NH	2,6-DMP[a]
pK_a[b]	16.8	18.2	18.5	18.9
β_{lg}	−0.23 ± 0.03	−0.25 ± 0.03	−0.18 ± 0.01	−0.23 ± 0.03

[a]*cis*-2,6-Dimethylpiperidine. [b]Reference 12.

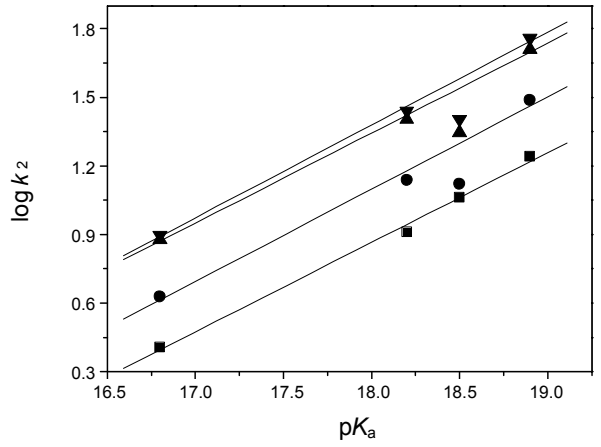


Figure 1. Brønsted plots for the elimination from (*E*)-2,4,6-$(NO_2)_3C_6H_2CH$=NOC(O)C_6H_4X Promoted by R_2NH in MeCN at 25.0 °C [X = H (**1a**, ●), *p*-OMe (**1b**, ■), *m*-Br (**1c**, ▲), *p*-CF_3 (**1d**, ▼)].

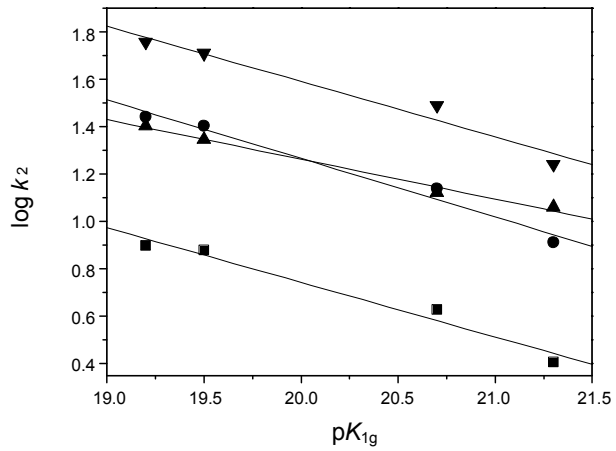


Figure 2. Plots log k_2 vs pK_{lg} values of the leaving group for the elimination from (*E*)-2,4,6-$(NO_2)_3C_6H_2CH$=NOC(O)C_6H_4X (**1a-d**) promoted by R_2NH in MeCN at 25.0 °C [R_2NH = Bz(*i*-Pr)NH (■), *i*-Bu_2NH (●), *i*-Pr_2NH (▲), 2,6-DMP (▼)].

Mechanism of elimination. Results of kinetic investigations and product studies clearly establish that the reaction of **1** with secondary amines produce the elimination products *via* an $(E1cb)_{irr}$ mechanism. Since the reactions exhibited second-order kinetics, all but bimolecular pathway could be ruled out. The observed general base catalysis with the Brönsted β values ranging from 0.39 ~ 0.41 rule out the $(E1cb)_R$, $(E1cb)_{ip}$, and internal return mechanisms because these mechanisms should exhibit either a specific base catalysis or Brönsted β values near unity.[11,14] Hence, the most likely mechanism for this bimolecular process is either E2 or $(E1cb)_{irr}$.

The distinction between the two mechanisms has been made by the interaction coefficients. The β and $|\beta_{lg}|$ values remained nearly the same within experimental error regardless of the ability of the leaving groups and the base strength variation (Tables 2 and 3). This effect corresponds to a negligible p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{lg} \approx 0$, which describes the interaction between the base catalyst and the leaving group.[11,15-18] The similar $|\beta_{lg}|$ values for all bases is another manifestation of this effect, that is, $p_{xy} = \partial\beta_{lg}/\partial pK_{BH} \approx 0$ (Table 3). The negligible interaction coefficients, $p_{xy} = \partial\beta/\partial pK_{lg} = \partial\beta_{lg}/\partial pK_{BH} \approx 0$, is consistent with the $(E1cb)_{irr}$ mechanism (*vide infra*).

The changes in the β and $|\beta_{lg}|$ values can be described by the More-O'Ferrall-Jencks reaction coordinate diagram (Figure 3).[15] On the More-O'Farrell-Jencks diagram depicted in Figure 3, a change to a better leaving group will raise the energy of the top edge of the diagram. The transition state on the horizontal coordinate will remain at nearly the same position resulting in a negligible change in β because there is no diagonal character. Similarly, a change to a stronger base will raise the energy of the right side of the diagram. The transition state on the horizontal coordinate will then move toward the right as depicted by a shift from A to B, resulting in little change in $|\beta_{lg}|$.[15] The negligible p_{xy} interaction coefficient is not consistent with an E2 mechanism for which $p_{xy} > 0$ is expected, but provides a

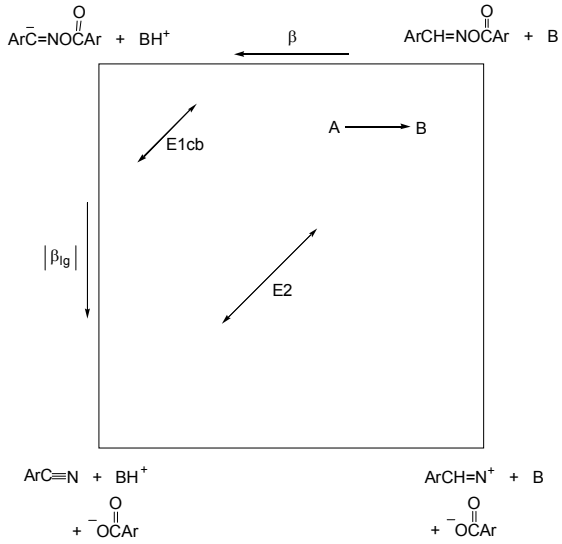


Figure 3. Reaction coordinate diagram for nitrile-forming elimination reactions from (*E*)-2,4,6-trinitrobenzaldehyde *O*-benzoyloximes. The effect of the change to a strongly electron-withdrawing β-aryl substituent are indicated by the shift of the transition state from A to B.

Table 4. Effect of β-aryl group on the nitrile-forming eliminations from (*E*)-ArCH=NOC(O)C_6H_5 promoted by R_2NH in MeCN at 25 °C

	Ar = 2,4-$(NO_2)_2C_6H_3$[b]	Ar = 2,4,6-$(NO_2)_3C_6H_2$
rel rate[a]	1	470
β	0.47 ± 0.04	0.40 ± 0.03
β_{lg}[b]	−0.36 ± 0.02	−0.25 ± 0.03
p_{xy}	> 0	~ 0

[a]Reference 6. [b]R_2NH = *i*-Bu_2NH.

strong evidence for the $(E1cb)_{irr}$ mechanism.[11,15-18]

Effect of β-aryl group. When the β-aryl group was changed from 2,4-dinitrophenyl to 2,4,6-trinitrophenyl, the rate increased by more than 470-fold and the Brönsted β and $|\beta_{lg}|$ values decreased, indicating the decrease in the extent of proton transfer and N_α-O(O)CAr bond cleavage in the transition state (Table 4). This result can be attributed to the enhanced anion stabilizing ability of β-aryl group. Since the partial negative charge developed at the β-carbon can be better stabilized by the strongly electron-withdrawing 2,4,6-trinitrophenyl group, the transition state should be less sensitive to the base strength variation, thereby decreasing the β value. Moreover, the negative charge developed at the β-carbon should be transferred to the α-nitrogen to form partial triple bond and to break the N_α-O(O)CAr bond. If a smaller amount of negative charge is transferred from the β-carbon, the extent of N_α-O(O)CAr bond rupture should be smaller too. This would predict a smaller $|\beta_{lg}|$ value, as observed.

In conclusion, we have studied the nitrile-forming elimination reactions from **1** promoted by R_2NH in MeCN. The reaction proceeded by $(E1cb)_{irr}$ mechanism. Change of the β-aryl group from 2,4-dinitrophenyl to a more strongly electron-withdrawing 2,4,6-trinitrophenyl increased the reaction rate by 470-fold, shifted the transition state toward more reactant-like, and changed the reaction mechanism from E2 to $(E1cb)_{irr}$. To the best of our knowledge, this is the first example of nitrile-forming elimination reaction that proceeds by the $(E1cb)_{irr}$ mechanism in MeCN. Noteworthy is the carbanion stabilizing ability of the 2,4,6-trinitrophenyl group in aprotic solvent.

Experimental Section

Materials. (*E*)-2,4,6-Trinitrobenzaldoxime was synthesized as reported previously.[1] All of the (*E*)-2,4,6-trinitrobenzaldehyde *O*-benzoyloxime derivatives **1a-d** were prepared in reasonable yields by adding the appropriate benzoyl chlorides (0.60 mmol) to the solution of (*E*)-2,4,6-trinitrobenzaldoxime (0.14 g, 0.50 mmol) in aqueous NaOH (0.4 M, 1.5 mL) solution at 0 °C. The solution was stirred for 20 ~ 30 min at 10 °C and poured into 10 mL of cold water. The product was recrystallized from ethanol. HRMS and elemental analysis results for **1a-d** could not be performed because they decomposed after several hours. However, the NMR data of the compounds were consistent with the proposed structures (Figures S2-S9, Supporting Information). The yield (%), melting point (°C), IR (KBr, C=O, cm^{-1}), ^1H NMR (400 MHz, acetone-d_6, *J* values are in Hz), and ^{13}C NMR (100 MHz, DMSO-d_6) spectral data for the new compounds are as follows.

(*E*)-2,4,6-$(O_2N)_3C_6H_2CH$=NOC(O)C_6H_5 (1a): Yield 85%; mp 190 °C; IR 1762; ^1H NMR δ 7.61-7.63 (m, 2H), 7.73-7.75 (m, 1H), 8.14-8.16 (m, 2H), 9.32 (s, 2H), 9.39 (s, 1H); ^{13}C NMR δ 124.1, 125.1, 127.1, 129.1, 129.5, 134.3, 148.5, 149.2, 152.9, 162.2.

(*E*)-2,4,6-$(O_2N)_3C_6H_2CH$=NOC(O)C_6H_4-*p*-OMe (1b): Yield 73%; mp 216 °C; IR 1772; ^1H NMR δ 3.93 (s, 3H), 7.11 (d, *J* = 9.16, 2H), 8.10 (d, *J* = 9.16, 2H), 9.31 (s, 2H), 9.34 (s, 1H); ^{13}C NMR δ 55.6, 114.4, 118.8, 124.0, 125.2, 131.8, 148.4, 149.2, 152.2, 161.8, 163.9.

(*E*)-2,4,6-$(O_2N)_3C_6H_2CH$=NOC(O)C_6H_4-*m*-Br (1c): Yield 57%; mp 240 °C; IR 1782; ^1H NMR δ 7.60 (t, *J* = 7.95, 1H), 7.93 (d, *J* = 7.95, 1H), 8.15 (d, *J* = 7.95, 1H), 8.30 (s, 1H), 9.33 (s, 2H), 9.45 (s, 1H); ^{13}C NMR δ 122.1, 124.0, 124.9, 128.6, 129.3, 131.2, 131.8,137.0, 148.4, 149.2,153.4,161.0.

(*E*)-2,4,6-$(O_2N)_3C_6H_2CH$=NOC(O)C_6H_4-*p*-CF_3 (1d): Yield 45%; mp 288 °C; IR 1744; ^1H NMR δ 7.83 (d, *J* = 8.08, 2H), 8.19 (d, *J* = 8.08, 2H), 9.28 (s, 2H), 9.40 (s, 1H); ^{13}C NMR δ 110.0, 124.3, 125.6, 130.1, 130.5, 132.3, 132.6, 134.6, 149.2, 151.2, 166.2.

Reagent-grade acetonitrile and secondary amines were fractionally distilled from CaH_2. The base-solvent solution was prepared by adding the appropriate amines to MeCN.

Kinetic studies. Reactions of **1** with R_2NH in MeCN were followed by monitoring the decrease in the absorbance of the substrate at 258 ~ 280 nm with a UV-vis spectrophotometer as described.[3,4]

Product studies. The product of eliminations from **1a** promoted by *i*-Bu_2NH in MeCN was identified by as described before.[6] The product was 2,4,6-trinitrobenzonitrile with mp 133 ~ 135 °C (lit.[19] mp 134 ~ 135 °C). The yield of 2,4,6-trinitrobenzonitrile was 93%.

Control experiment. The stabilities of **1a-d** were determined as reported.[4,6] The solutions of **1** in MeCN were stable for at least five weeks when stored in the refrigerator.

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Supporting Information Available. Observed rate constants for elimination from **1a** promoted by *i*-Pr_2NH in MeCN, Plot of k_{obs} *vs* base concentration, and NMR spectra for all new compounds are available on request from the correspondence author (5pages). e-mail: sypyun@pknu.ac.kr.

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