ISSN 0023-1584, Kinetics and Catalysis, 2011, Vol. 52, No. 3, pp. 371–375. © Pleiades Publishing, Ltd., 2011.

Elimination of Nitrile from (E)-2,4,6-Trinitrobenzaldehyde O-Pivaloyloxime Promoted by R_2NH in MeCN. Effect of β-Aryl Group on the Nitrile-Forming Transition-State[1]

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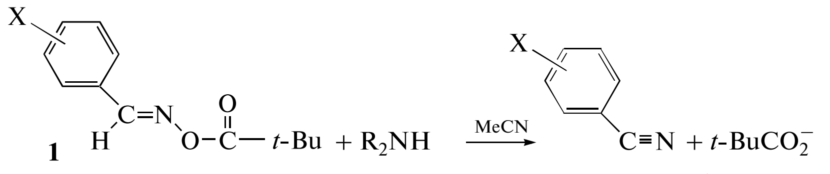
Received November 27, 2009

Abstract—Nitrile-forming eliminations from (E)-2,4,6-$(NO_2)_3C_6H_2CH{=}NOC(O)(CH_3)_3$ promoted by R_2NH in MeCN have been studied kinetically. The reactions are second-order and exhibit substantial Hammett ρ and Brönsted β values. The k_2 value for elimination from (E)-2,4,6-trinitrobenzaldehyde O-pivaloyloxime promoted by i-Pr_2NH in MeCN falls on a single line in the Hammett plot for different β-aryl substituents, which have been shown to react by the E2 mechanism. This result indicated that the reaction mechanism is not changed by the introduction of the 2,4,6-trinitro substituents, and that the elimination reactions from (E)-benzaldehyde O-pivaloyloximes series proceed by the common E2 mechanism.

DOI: 10.1134/S0023158411030165

Elimination reactions from (E)-benzaldehyde O-pivaloyloxime have been extensively investigated under various conditions [1–3]. In all cases, the reactions proceeded by the E2 mechanism in MeCN despite the fact that the reactants have *syn*-stereochemistry, poor leaving group, and sp^2 hybridized β-carbon atom, all of which favor the E1cb- or E1cb-like transition state [4–7]. Moreover, the transition states 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. In contrast, for eliminations from strongly activated (E)-2,4-dinitrobenzaldehyde O-benzoyloxime, 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) [8]. A combination of a strong electron-withdrawing β-aryl group and anion-solvating protic solvent was required for the mechanistic change. The pK_a of benzoic acid in MeCN is 20.7, which is similar to that of the pivaloic acid [3, 9]. This would predict that the pivaloate could be a similar leaving group as benzoate. Therefore, the reactions of (E)-2,4-dinitrobenzaldehyde O-pivaloyloxime with $R_2NH/R_2NH_2^+$ in 70 mol % MeCN(aq) may proceeded by the E1cb mechanism. However, the reaction proceeded by the E2 mechanism [3].

We were interested in learning, if a change to the Elcb mechanism could be realized in aprotic solvent by making the β-aryl substituent even more electron-withdrawing. To explore such possibility, we studied the reaction of (E)-2,4,6-trinitrobenzaldehyde O-pivaloyloxime with R_2NH in MeCN (Eq. (1)). This substrate is most strongly activated one studied so far in (E)-benzaldehyde O-pivaloyloxime series. By comparing with the existing data for eliminations from arylbenzaldehyde O-pivaloyloxime, the effect of β-aryl substituent was assessed.



(1)

X=H (**a**), p-OCH_3 (**b**), m-Br (**c**), p-NO_2 (**d**), 2,4-$(NO_2)_2$ (**e**), 2,4,6-$(NO_2)_2$ (**f**)
R_2NH=Bz(i-Pr)NH, i-Bu_2NH, i-Pr_2NH, 2,6-DMP.

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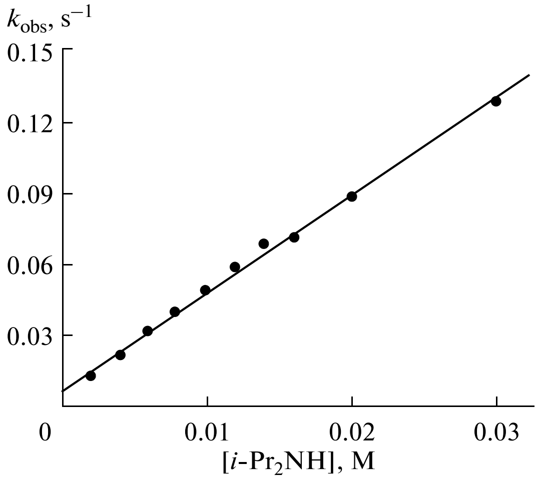

Fig. 1. Plot of k_{obs} vs. base concentration for the reaction of (E)-2,4,6-$(NO_2)_3C_6H_2CH{=}NOC(O)C(CH_3)_3$ promoted by i-Pr_2NH in MeCN at 25°C.

EXPERIMENTAL

Materials. (E)-Benzaldehyde O-pivaloyloximes **1a–e** were available from previous work. The compounds were again recrystallized from ethanol. Freshly purified compounds were used in all kinetics runs. (E)-2,4,6-trinitrobenzaldehyde O-pivaloyloxime (**1f**) was prepared in reasonable yield by adding the pivaloyl chloride (0.6 mmol) to the solution of (E)-2,4,6-trinitrobenzaldoxime (0.14 g, 0.5 mmol) in aqueous NaOH solution (0.4 M, 1.5 ml) at 0°C as described previously [1]. The solution was stirred for 20–30 min at 10°C and poured into 10 ml of cold water. The products were recrystallized from ethanol. HRMS and elemental analysis results for **1f** could not be performed because they decomposed after several hours. However, the NMR data of the compound was consistent with the proposed structure. The yield (%), melting point (°C), IR (KBr, C=O, cm^{-1}), ^1H NMR (400 MHz, Acetone-d_6), and ^{13}C NMR (100 MHz, DMSO-d_6) spectral data for the new compounds are as follows. Yield 91%; mp 243°C; IR 1763 cm^{-1}; ^1H NMR δ 2.05 (s, 9H), 9.15 (s, 1H), 9.28 (s, 2H); ^{13}C NMR δ 27.1, 38.4, 123.8, 127.4, 148.4, 148.8, 150.5, 174.2.

Table 1. The first-order rate constants for elimination from (E)-2,4,6-$(NO_2)_3C_6H_2CH{=}NOC(O)C(CH_3)$ (5.0×10^{-5} mol l^{-1}) promoted by i-Pr_2NH in MeCN at 25°C

10^2 [i-Pr_2NH], mole l^{-1}	10^2 k_{obs}, $s^{-1\,b,\,c}$
0.2	1.17
0.4	2.10
0.6	3.12
0.8	3.95
1.0	4.82
1.2	5.81
1.4	6.81
1.6	7.03
2.0	8.73
3.0	12.7

Reagent grade acetonitrile and secondary amines (R_1R_2=Bz(i-Pr)NH (benzylisopropylamine), i-Bu_2NH (diisobutylamine), i-Pr_2NH (diisopropylamine), 2,6-DMP (2,6-dimethylpiperidine), were fractionally distilled over CaH_2. The MeCN solution of amine was prepared by adding appropriate amounts of amine 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 268–280 nm with a UV-vis spectrophotometer as described elsewhere [1–3]. On the other hand, the rates of the reactions of **1f** were too fast to follow to completion. Therefore, the rate studies utilized a stopped-flow spectrophotometer. However, the k_{obs} values calculated from the slopes of the plots were in excellent agreement (within ±5%) with the k_{obs} calculated by using a UV-vis spectrophotometer. All rate constants were average from at least three experiments.

Product studies. The products of the reactions of **1a** and **1f** with i-Bu_2NH in MeCN were identified by GC-MS and melting point. A solution of 0.30 g (1.47 mmol) of **1a** and an excess amount of base (15 ml) was stirred for 10 hrs at room temperature. The solvent was removed *in vacuo*, and the residue was extracted with CH_2Cl_2 and washed thoroughly with water until all of the amine, ammomium salt, and benzoate were completely removed. The yield of PhC≡N (94%) was determined by GC. The product studies of **1f** with i-Bu_2NH in MeCN was also carried out as described above. The product was 2,4,6-trinitrobenzonitrile with mp 133–135°C (mp 134–135°C [10]). The yield of 2,4,6-trinitrobenzonitrile was 92%.

Control experiments. The stabilities of **1** were determined as reported [2]. The solutions of **1a–e** in MeCN were stable for at least 4 weeks, when stored in the refrigerator. They were stable for a long time in the solid state. However, MeCN solution of **1f** was stable for only several hours.

RESULTS

The reactions of **1a** and **1f** with i-Bu_2NH in MeCN produced benzonitrile and 2,4,6-trinitrobenzonitrile, respectively. The yields of products were 94 and 92%, respectively. No trace of benzaldehyde oximes could be detected by TLC.

The kinetics of the elimination reaction for **1e** and **1f** measured from the disappearance of the substrate absorption at 280 nm show excellent pseudo-first order kinetic plots that covered at least two half-lives. However, the rates of the reactions of **1a–d** were too slow to follow to completion. Therefore, initial rate method was employed [11].

The observed rate constants for eliminations from **1f** are listed in Table 1. Plot of k_{obs} for the reaction of **1f**

Table 2. The rate constants for elimination from (E)-$ArC_6H_2CH{=}NOC(O)C(CH_3)$ (8.0×10^{-5} mol l^{-1}) promoted by R_2NH (1.0×10^{-3}–3.0×10^{-2} mol l^{-1}) in MeCN at 25.0°C

Ar	R_2NH	pK_a [9]	σ^- [12, 13]	k_2, l mol^{-1} s^{-1}
4-MeO	i-Pr_2NH	18.5	–0.27	$(2.24 \pm 0.02) \times 10^{-6}$
H	i-Pr_2NH	18.5	0	$(5.37 \pm 0.14) \times 10^{-6}$
3-Br	i-Pr_2NH	18.5	0.39	$(7.82 \pm 0.05) \times 10^{-6}$
4-NO_2	i-Pr_2NH	18.5	1.23(0.78)[a]	$(2.24 \pm 0.02) \times 10^{-3}$
2,4-NO_2	i-Pr_2NH	18.5	2.48(1.56)[a]	$(7.93 \pm 0.02) \times 10^{-3}$
2,4,6-NO_2	Bz(i-Pr)NH[c]	16.8	4.72(2.34)[a]	$(6.40 \pm 0.06) \times 10^{-2}$
2,4,6-NO_2	i-Bu_2NH[d]	18.2	4.72	(2.48 ± 0.02)
2,4,6-NO_2	i-Pr_2NH[e]	18.5	4.72	(4.08 ± 0.02)[b]
2,4,6-NO_2	2,6-DMP[f]	18.9	4.72	(8.88 ± 0.01)

[a] σ values. [b] $k_0 = 6.42 \times 10^{-3}$ s^{-1}. [c] Benzylisopropylamine. [d] Diisobutylamine. [e] Diisopropylamine . [f] 2,6-Dimethylpiperidine.

with i-Pr_2NH in MeCN against the base concentration was straight line positive intercept (Fig. 1). This indicates that the rate equation for the reactions of **1f** is $k_{obs} = k_0 + k_2 [R_2NH]$. The slope and intercept of this straight line was calculated by linear regression. The second-order rate constant (k_2) and zero-order rate constant (k_0) were determined from the slope and intercept of the straight line. For reaction of **1f** with i-Pr_2NH, the k_2 = 4.08 l mol^{-1} s^{-1} and $k_0 = 6.42 \times 10^{-3}$ s^{-1} were obtained from the slope and the intercept of the plot. Thus, the solvolytic elimination of **1f** becomes negligible. Therefore, the rate constants for the base-promoted eliminations from compounds **1a–e** were determined at a single base concentration. The k_2 values were calculated by dividing the k_{obs} values by the base concentration. The second-order rate constants thus determined were listed in Table 2. The rates increase as the electron-withdrawing ability of the β-aryl substituents increases.

Hammett plots of log k_2 vs. σ^- and σ values are depicted in Fig. 2. The rate data correlated better with σ^- rather than σ parameters. Hammett ρ value is 1.26 ± 0.04 and 2.94 ± 0.42 for 1, respectively. The k_2 values showed excellent correlation with the pK_a values of the promoting base on the Brönsted plot (Fig. 3). For R_2NH promoted eliminations from **1f**, the value of $\beta = 0.52 \pm 0.07$.

DISCUSSION

Mechanism of elimination. Earlier it was established that the elimination reactions of (E)-benzaldehyde O-pivaloyloximes with DBU–MeCN, Et_3N–MeCN, t-BuOK–t-BuOH, and t-BuOK–DMSO proceeded by an E2 mechanism [1, 2]. The results of the product and kinetic studies revealed that the reactions of **1a–e** with $R_2NH/R_2NH_2^+$ in 70 mol % MeCN(aq) also proceeded by the same mechanism [3]. On the other hand, it is conceivable that an increase in the electron-withdrawing ability of the β-aryl-substituent would lower the energy of the carbanion intermediate, which may in turn change the reaction mechanism to E1cb. To assess this possibility, we have investigated elimination reaction reactions of **1f** with R_2NH in MeCN. The rate equation for the reactions can be expressed as $k_{obs} = k_0 + k_2 [R_2NH]$. This result reveals that the reactions must proceed via competing solvolytic (k_0) and bimolecular (k_2) elimination pathways and the former becomes negligible at MeCN solvent ($k_2 = 4.08$ l mol^{-1} s^{-1}, $k_0 = 6.42 \times 10^{-3}$ s^{-1}). In addition, for elimination of **1f**, the value of β = 0.52 was determined.

Since the elimination reactions exhibit second-order kinetics and substantial value of β was determined, all but E2 and $(E1cb)_{irr}$ mechanisms can be ruled out [14]. The distinction between these two mechanisms can readily be interpreted by the leaving group effect. The $(E1cb)_{irr}$ mechanism would predict that the leaving group element effect should be near unity (or $|\beta_{lg}| = 0$), because the bond to the leaving group remains intact in the rate limiting step. In contrast, much larger leaving group is anticipated for the E2, because the N_α–$OC(O)C(CH_3)_3$ bond must be broken significantly in the transition state. However, the distinction between these two mechanisms cannot be made due to the lack of the data for the effect of leaving group. The distinction between these two mechanisms can readily be made by the Hammett plot and interaction coefficients. Earlier we reported a kinetic investigation of the nitrile-forming elimination from (E)-benzaldehyde O-pivaloyloximes promoted by DBU (pK_a = 19.4) in MeCN [3], Hammett ρ value of 2.40 has been determined. On the other hand, for R_2NH-promoted eliminations from **1**, value of ρ = 1.26 was determined. This result shows that the Hammett ρ value for eliminations from **1** decreases from

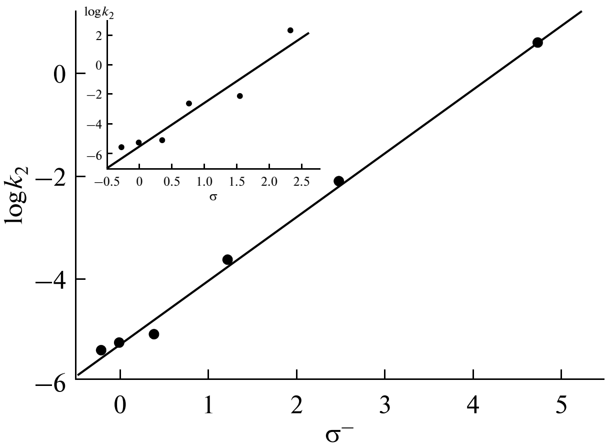

Fig. 2. The Hammett plot for the elimination from $ArCH{=}NOC(O)C(CH_3)_3$ promoted by $i\text{-}Pr_2NH$ in MeCN at 25°C. A plot of log k_2 vs. σ is shown in the inset.

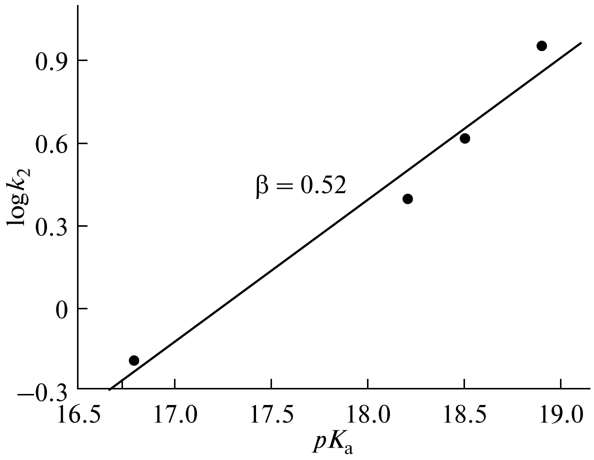

Fig. 3. The Brönsted plot for the elimination from (E)-$2,4,6\text{-}(NO_2)_3C_6H_2CH{=}NOC(O)C(CH_3)_3$ promoted by R_2NH in MeCN at 25°C.

2.40 to 1.26 as the basicity of the promoting base is decreased.

The result can be described by a positive p_{xy} interaction coefficient, $p_{xy} = \partial\rho/\partial pK_a$, that describes the interaction between the base catalyst and the β-aryl substituent [3, 7, 11, 15]. The positive p_{xy} interaction coefficient is not consistent with an E1cb mechanism for which $p_{xy} < 0$ is expected, but provides a strong support for the concerted E2 mechanism. This conclusion is also support by the Hammett plot for eliminations from **1** promoted by $i\text{-}Pr_2NH$ in MeCN (Fig. 2). Figure 2 shows that the k_2 values for elimination from **1f** promoted by $i\text{-}Pr_2NH$ in MeCN falls on a single line for **1a–e**, which have been shown to react by the E2 mechanism. On the other hand, we reported the nitrile-forming elimination from **1** with R_2NH in 70 mol % MeCN(aq) proceeded via an E2 mechanism [3]. Values of ρ =1.06 (it has again been made to the ρ values in the Hammett plots of the rate data measured in 70 mol % MeCN(aq). The rate data correlated better with σ$^-$ rather than σ parameters. Hammett ρ values were 1.06 ± 0.1 ($R^2 = 0.986$) and 1.63 ± 0.20 ($R^2 = 0.977$) for **1a–e**, respectively) and β = 0.45 were determined. When the solvent was changed from 70 mol % MeCN(aq) to MeCN, the ρ value increased from 1.06 to 1.24 and the β value increased slightly from 0.45 to 0.52. Both the Hammett ρ and β values increase, indicating enhancement in the negative charge density at the β-carbon, and the extent of C_β–H bond cleavage in the transition state as the solvent is changed to MeCN. The result may be attributed to a solvation effect. Since the partial negative charge developed on the β-carbon in the transition state cannot be stabilized by solvation in poorly anion-solvating medium MeCN, the transition state should more sensitive to the electron-withdrawing ability of the aryl substituent and to the base strength. This would predict a greater ρ and β values, as observed. However, the transition state for the nitrile-forming elimination from **1** appear to very similar for both base-solvent systems. Therefore, it seems reasonable to ascribe an E2 mechanism to reactions of **1** with R_2NH in MeCN. This result indicates that the mechanism is not changed by the introduction of the strongly electron-withdrawing substituent, and that the elimination reactions from **1a–f** proceed by the common E2 mechanism.

Effect of β-aryl group on the nitrile-forming transition state. It is conceivable that a strong electron-withdrawing β-aryl substituent may decrease the energy of the carbanion intermediate lower than that of the E2 transition state to induce a change in the reaction mechanism. However, no change in the reaction mechanism has been realized by the 2,4,6-trinitro-substituents, despite the most strongly activated one studied so far in the (E)-benzaldehyde O-pivaloyloximes series. These results may be attributed to the geometry of the reactant structure. It has been well established that the benzaldoxime esters have planar structures [2, 16, 17]. Therefore, if the planarity is retained in the transition state, the π orbitals of the β-aryl group should be nearly orthogonal to the developing negative charge at the β-carbon in the transition state [17]. This would predict that the electronic effect of the β-substituent should be transmitted to the reaction site only through an inductive effect.

In conclusion, the nitrile-forming eliminations from **1f** proceed by the E2 mechanism. Noteworthy is the relative insensitiveness of the nitrile-forming transition state to the structural variations of the β-aryl substituent.

This work was supported by the Pukyong National University Research Fund in 2009 (PK-2009-23).

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