

Ketene-forming elimination reactions from aryl phenylacetates promoted by R_2NH in MeCN: effects of base-solvent and β -phenyl group

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Received 21 March 2007; revised 22 May 2007; accepted 23 May 2007

ABSTRACT: Elimination reactions of $C_6H_5C(R)HCO_2C_6H_3-2-X-4-NO_2$ [$R = H$ (**1**), Ph (**2**), $X = H$ (**a**), Cl (**b**), NO_2 (**c**)] promoted by R_2NH in MeCN have been studied kinetically. The reactions are second-order and exhibit Brønsted $\beta = 0.46$ – 0.89 and $|\beta_{lg}| = 0.37$ – 0.76 and an E2 mechanism is evident. When the base-solvent was changed from $R_2NH/R_2NH_2^+-70$ mol% MeCN(aq) to R_2NH -MeCN, β and $|\beta_{lg}|$ values remained nearly the same within experimental error. For eliminations from **1** and **2**, β and $|\beta_{lg}|$ values were nearly identical, although the rate was retarded by the β -Ph group. Noteworthy is the relative insensitivity of the ketene-forming transition state to the base-solvent and β -R group variation. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: elimination; E2; E1cb; base-solvent

INTRODUCTION

Extensive studies on the base catalyzed reactions of aryl phenylacetates provided a rich mechanistic diversity ranging from hydrolysis to ketene-forming elimination reactions.^{1–14} When hydroxide or alkoxide was used as the base in protic solvents, the reaction proceeded by the hydrolysis mechanism. With amine bases in aprotic solvent, however, the elimination became predominant reaction pathway. One of the most interesting results from these studies is the discovery of competing E2 and E1cb mechanisms in eliminations from *p*-nitrophenyl *p*-nitrophenylacetates promoted by $R_2NH/R_2NH_2^+$ in 70 mol% MeCN(aq).¹⁴ A gradual change of the mechanism from E2 to E1cb via a competing mechanism has been demonstrated by systematically varying the structure of 2-Y-4- $NO_2C_6H_3CH_2CO_2C_6H_3-2-X-4-NO_2$.¹⁵ Thus, the transition state became more E1cb-like as the leaving group was made poorer, and the E1cb mechanism emerged when $X, Y = H$. The E1cb mechanism became predominant when $X = H$ and $Y = NO_2$, probably because the carbanion intermediate was stabilized by

the strongly electron-withdrawing substituent and the E2 mechanism could no longer compete.

Earlier, we reported that the ketene-forming elimination from Ph_2CHCO_2Ar promoted by $R_2NH/R_2NH_2^+-70$ mol% MeCN(aq) proceeded via an E2-central transition state, with similar extents of $C_\beta-H$ and $C_\alpha-OAr$ bond cleavage.¹⁶ Comparison of the transition state parameters revealed that the extent of proton transfer decreased and the degree of the leaving group bond cleavage increased by the change of the substrate from $PhCH_2CO_2Ar$ to Ph_2CHCO_2Ar . The result was attributed to the double bond stabilizing effect of the β -Ph group. Because the phenyl group can stabilize the $C=C$ bond, more of the electron density on the β -carbon would be transferred toward the $C_\beta-C_\alpha$ bond to increase the transition-state double bond character for maximum stabilization.

To further enhance our understanding on the ketene-forming eliminations, we have investigated the reactions of aryl phenylacetates **1** and **2** with R_2NH -MeCN [Eqn (1)]. We thought that the transition state double bond character would increase in MeCN because the developing negative charge can not be stabilized by solvation.^{14,16–18} Therefore, it would be interesting to compare the β -Ph group effect on the ketene-forming transition state under different conditions. Comparison with existing data¹⁶ for the reactions of **1** and **2** with $R_2NH/R_2NH_2^+-70$ mol% MeCN(aq) revealed the

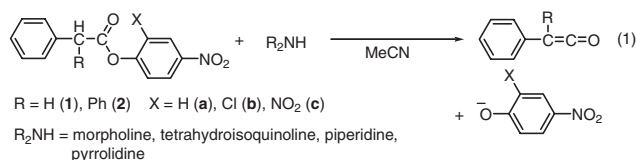
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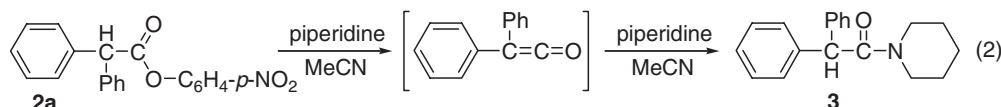
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effects of the base-solvent and β -Ph group variations on the ketene-forming eliminations.



RESULTS

Aryl phenylacetates **1**, **2** were available from previous studies.¹⁶ The product of the reaction between **2a** and piperidine in MeCN was identified as described.¹⁴ From this reaction, 3,3-diphenylpropionic acid piperidylamide (**3**) was obtained in 89% yield [Eqn (2)].



When the reactions of **1a–c** and **2a–c** with R₂NH in MeCN were monitored, the absorbance corresponding to the reactant at 240–260 nm decreased, while that for the aryloxides increased at 428–430 nm. Clean isobestic points were observed at 289–300 nm. For elimination reactions from **1a–c** and **2a–c**, the yields of the aryloxides as determined by comparing the infinity absorbance of the samples from the kinetic studies with those of the authentic aryloxides were in the range of 93–96%. The possibility of competing aminolysis had been ruled as previously reported.¹⁴

Reactions of **1** and **2** with R₂NH in MeCN were followed by monitoring the increase in the absorbance of

the aryloxides at 428–430 nm with a UV–Vis spectrophotometer as described.^{14,16,19} Excellent pseudo-first-order kinetic plots, which covered at least three half-lives, were obtained. The plots of k_{obs} versus base concentration for **1** and **2** 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 (plots not shown). The second-order rate constants k_2 were obtained either from the slopes of straight lines or by dividing the k_{obs} by the base concentration. Values of k_2 for eliminations from **1** and **2** are summarized in Table 1.

The k_2 values showed excellent correlation with the $\text{p}K_{\text{a}}$ values of the promoting base on the Brønsted plot (Figs 1 and 2). The β value decreased as the leaving group was made less basic (Table 2). Similarly, the k_2 values correlated satisfactorily with the leaving group $\text{p}K_{\text{a}}$ values (Figs 3 and 4). The $|\beta_{\text{lg}}|$ value decreased with a stronger base (Table 3).

DISCUSSION

Mechanism of elimination from **1** and **2** promoted by R₂NH in MeCN

Results of kinetic investigations and product studies clearly establish that the reactions of aryl phenylacetates **1** and **2** with R₂NH in MeCN proceed by the E2 mechanism. An addition-elimination mechanism (B_{AC2}) is ruled out by the negligible rates of aminolysis compared with the overall rates as reported previously.¹⁴

Table 1. Rate constants for eliminations from PhCH(R)CO₂C₆H₃-2-X-4-NO^a promoted by R₂NH MeCN^b at 25.0 °C

Base	$\text{p}K_{\text{a}}^{\text{c}}$	$k_2 \text{ (M}^{-1}\text{s}^{-1})^{\text{d,e}}$					
		1a	1b	1c	2a	2b	2c
Morpholine	16.6	0.0438	2.88	69.6	0.00864	0.514	33.4
THIQ ^f	17.1	0.101	4.99	104	0.0199	0.848	45.9
Piperidine	18.9	2.11	67.9	749	0.374	14.4	456
Pyrrolidine	19.6	28.2	459	1620	5.89	142	1548

^a [Substrate] = 3.0×10^{-5} M.

^b [Base] = 4.0×10^{-4} – 1.0×10^{-1} M.

^c References [23 and 24].

^d Average of three or more rate constants.

^e Estimated uncertainty, $\pm 3\%$.

^f 1,2,3,4-Tetrahydroisoquinoline.

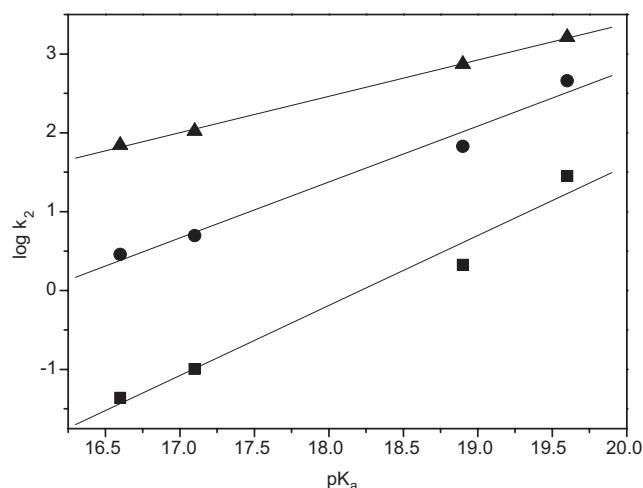


Figure 1. Brønsted plots for the ketene-forming eliminations from aryl phenylacetates [$\text{PhCH}_2\text{CO}_2\text{C}_6\text{H}_3\text{-2-X-4-NO}_2$] promoted by R_2NH in MeCN at 25.0°C [$\text{X} = \text{H}$ (■), Cl (●), NO_2 (▲)].

Since the reactions produced only elimination products and exhibited second-order kinetics, all but bimolecular pathways can be ruled out. In addition, an E1cb mechanism is negated by the substantial values of β and $|\beta_{\text{lg}}|$.^{20–22}

This conclusion is supported by the interaction coefficients. Table 2 shows that the β values for **1** decrease gradually as the leaving groups are made less basic. The result can be described by a positive p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial\text{p}K_{\text{lg}} = \partial\beta_{\text{lg}}/\partial\text{p}K_{\text{BH}}$, that describes the interaction between the base catalyst and the leaving group.^{20–22} The observed increase in the $|\beta_{\text{lg}}|$

Table 2. Brønsted β values for ketene-forming eliminations from $\text{PhCH(R)CO}_2\text{C}_6\text{H}_3\text{-2-X-4-NO}$ promoted by R_2NH in MeCN at 25.0°C

X	$\text{p}K_{\text{a}}^{\text{a}}$	β	
		R = H (1)	R = Ph (2)
H	20.7	0.89 ± 0.10	0.89 ± 0.12
Cl	18.6	0.71 ± 0.07	0.79 ± 0.09
NO_2	16.0	0.46 ± 0.01	0.56 ± 0.04

^a Reference [23].

values as the catalyst is less basic is another manifestation of this effect, i.e., $p_{xy} = \partial\beta_{\text{lg}}/\partial\text{p}K_{\text{BH}} > 0$. On the More-O'Ferall–Jencks energy diagram in Fig. 5, a change to a poorer leaving group will raise the energy of the bottom edge of the diagram shifting the transition state toward the product and E1cb intermediate. The transition state will then move toward the left as depicted by a shift from A to B on the energy diagram, resulting in an increase in β (*vide supra*).^{20–22} Similarly, a weaker base will raise the energy of the left side of the energy diagram and shift the transition state from A to C to increase the extent of $\text{C}_\alpha\text{—OAr}$ bond cleavage and $|\beta_{\text{lg}}|$. The positive p_{xy} coefficients are inconsistent with an E1cb mechanism for which $p_{xy} = 0$ is expected, but provide additional support for the concerted E2 mechanism.^{20–22} Similar interpretation can be put forwarded to the changes in β and $|\beta_{\text{lg}}|$ values with the leaving group and base strength variations for **2**.

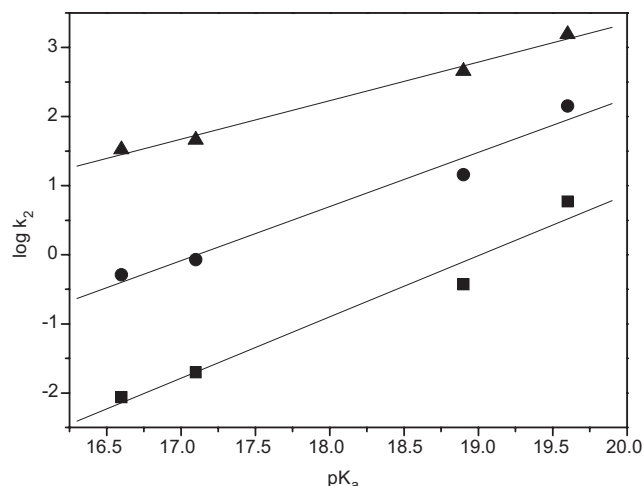


Figure 2. Brønsted plots for the ketene-forming eliminations from aryl diphenylacetates [$\text{Ph}_2\text{CHCO}_2\text{C}_6\text{H}_3\text{-2-X-4-NO}_2$] promoted by R_2NH in MeCN at 25.0°C [$\text{X} = \text{H}$ (■), Cl (●), NO_2 (▲)].

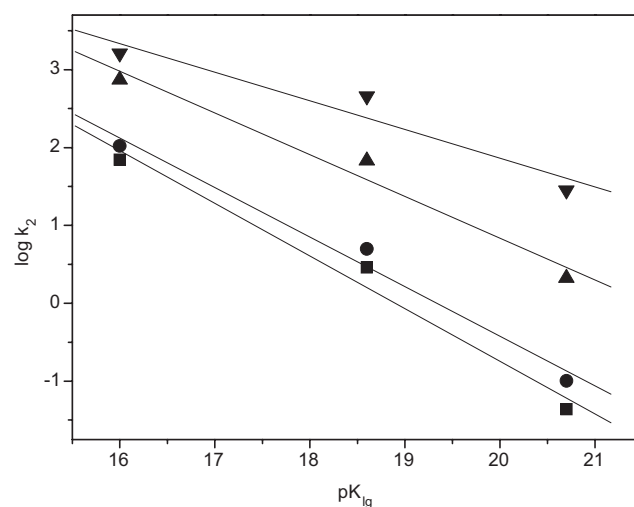


Figure 3. Plots of $\log k_2$ versus $\text{p}K_{\text{lg}}$ values for the ketene-forming eliminations from aryl phenylacetates [$\text{PhCH}_2\text{CO}_2\text{C}_6\text{H}_3\text{-2-X-4-NO}_2$] promoted by R_2NH in MeCN at 25.0°C [$\text{R}_2\text{NH} = \text{morpholine}$ (■), $\text{tetrahydroisoquinoline}$ (●), piperidine (▲), pyrrolidine (▼)].

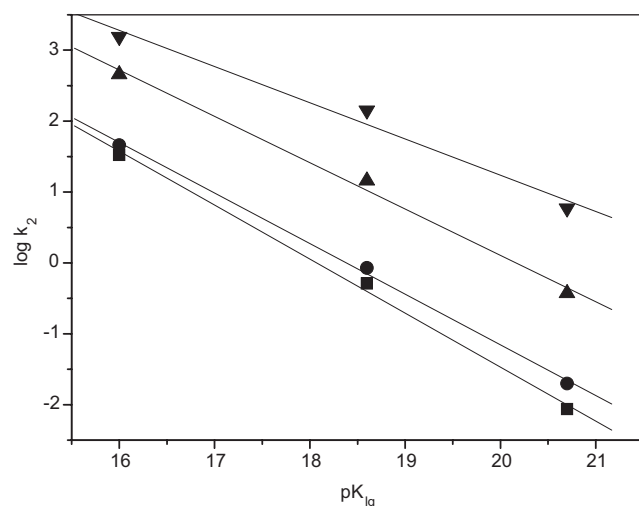


Figure 4. Plots of $\log k_2$ versus pK_{lg} values for the ketene-forming eliminations from aryl diphenylacetates [$\text{Ph}_2\text{CHCO}_2\text{C}_6\text{H}_3-2\text{-X-4-NO}_2$] promoted by R_2NH in MeCN at 25.0°C [R_2NH = morpholine (■), tetrahydroisoquinoline (●), piperidine (▲), pyrrolidine (▼)].

Effects of base-solvent and β -phenyl group on the ketene-forming transition state

For R_2NH -promoted eliminations from **1**, the rate increased slightly and the values of β and $|\beta_{lg}|$ remained nearly the same within experimental error as the base-

Table 3. Brønsted β_{lg} values for ketene-forming eliminations from $\text{PhCH(R)CO}_2\text{C}_6\text{H}_3-2\text{-X-4-NO}$ promoted by R_2NH in MeCN at 25.0°C

Base	pK_a^a	β_{lg}	
		R = H (1)	R = Ph (2)
Morpholine	16.6	-0.68 ± 0.09	-0.76 ± 0.04
THIQ ^b	17.1	-0.64 ± 0.08	-0.71 ± 0.03
Piperidine	18.9	-0.54 ± 0.09	-0.65 ± 0.05
Pyrrolidine	19.6	-0.37 ± 0.10	-0.51 ± 0.07

^a References [23 and 24].

^b Tetrahydroisoquinoline.

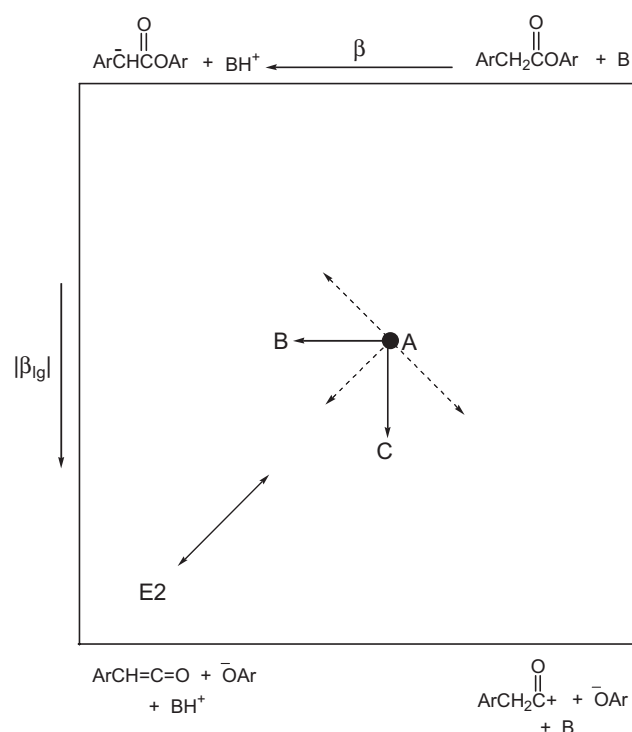


Figure 5. Reaction coordinate diagram for the ketene-forming elimination. The effect of the change to a poorer leaving group and a weaker base are shown by the shift of the transition state from A to B and A to C, respectively.

solvent system was changed from $\text{R}_2\text{NH}/\text{R}_2\text{NH}_2^+-70\text{ mol\% MeCN(aq)}$ to $\text{R}_2\text{NH-MeCN}$ (Table 4). A similar result was observed for **2** except that the extent of proton transfer was slightly increased. The slight increase in rate can be attributed to the enhanced basicity in more hydrophobic MeCN. On the other hand, the similar values of β and $|\beta_{lg}|$ indicate the relatively insensitivity of the ketene-forming transition state to the base-solvent variation. Because the developing negative density at the β -carbon can be stabilized either by the β -Ph group (in MeCN) or by the oxygen atoms of carbonyl and leaving group [in 70 mol% MeCN(aq)] (*vide infra*), the anion-solvating ability of the solvent appears to be less important.

Table 4. Effect of base-solvent and β -R group on the ketene-forming eliminations from $\text{PhCH(R)CO}_2\text{C}_6\text{H}_5-4\text{-NO}$ at 25.0°C

Base-solvent	R = H (1)		R = Ph (2)	
	MeCN(aq) ^{a,b}	MeCN ^{c,d}	MeCN(aq) ^{a,b}	MeCN ^{c,d}
Relative rate ^e	1.0	1.6	1.0	3.6
β	0.78 ± 0.04	0.89 ± 0.10	0.67 ± 0.03	0.89 ± 0.12
β_{lg}^e	-0.40 ± 0.03	-0.54 ± 0.09	-0.57 ± 0.04	-0.65 ± 0.05

^a $\text{R}_2\text{NH}/\text{R}_2\text{NH}_2^+$ in 70 mol% MeCN(aq).

^b Reference [16].

^c R_2NH in MeCN(aq).

^d This work.

^e R_2NH = piperidine.

When the β -R group was changed from H to Ph for R_2NH -promoted eliminations from **1** and **2** in MeCN, β and $|\beta_{lg}|$ values remained nearly the same, although the rate was retarded by the Ph-group probably because of the steric effect. Here again, the relative insensitivity of the ketene-forming transition state to the β -R group variation is noted. On the other hand, when the same reactions were carried out in $R_2NH/R_2NH_2^+-70\text{ mol\% MeCN(aq)}$, the extent of proton transfer decreased and the degree of C_α —OAr bond cleavage increased by the same variation of the β -R group. The difference between the β -R group effects in the two base-solvent systems can be attributed to the anion-solvating ability of the solvent. In 70 mol% MeCN(aq), where the developing negative charge on the leaving group oxygen atom can be stabilized by forming a stronger hydrogen bonding with water and $R_2NH_2^+$, a significant amount of charge density could be transferred toward the C_β — C_α bond to enhance the double bond character and increase the charge density on the leaving group oxygen atom. The transition state would then be more symmetrical with similar extents of C_β —H and C_α —OAr bond cleavage and more double bond character. In MeCN, however, the charge density at the β -carbon may be stabilized by the β -Ph group rather than to transfer toward the C_β — C_α bond to form the partial double bond because the leaving group oxygen atom cannot be stabilized by hydrogen bonding. This would predict that the transition state structure would not be significantly altered and the extents of C_β —H and C_α —OAr bond cleavage would remain nearly the same.

In conclusion, we have studied the ketene-forming elimination reactions from **1** and **2** promoted by R_2NH in MeCN. The reactions proceed by the E2 mechanism via the E2-central transition state. Noteworthy is the relative insensitivity of the transition state to the base-solvent and β -R group variation.

EXPERIMENTAL

Materials

Aryl phenylacetates **1** and **2** were available from previous studies.¹⁶ Reagent grade acetonitrile and secondary amines were fractionally distilled from CaH_2 . The solutions of R_2NH in MeCN were prepared by dissolving R_2NH in MeCN.

Kinetic studies

Reactions of **1** and **2** with R_2NH in MeCN were followed by monitoring the increase in the absorbance of the aryloxides at 428–430 nm with a UV–Vis spectrophotometer as described.^{14,16,19}

Product studies

The product of the reaction between **2a** and piperidine in MeCN was identified as described.¹⁴ From this reaction, 3,3-diphenylpropionic acid piperidylamide (**3**) was obtained in 89% yield. For all reactions, the yields of aryloxides as determined by comparing the absorbance of the infinity absorbance of the samples from the kinetic studies with those of the authentic aryloxides were in the range of 96–99%.

Control experiments. The stabilities of **1** and **2** were determined as reported.^{14,16,19} Solutions of aryl phenylacetates **1a**, **1b**, **2a**, and **2b** were stable for at least 2 weeks in MeCN solution at room temperature. However, the solutions of **1c** and **2c** were stable for only 6 days.

Acknowledgement

This work was supported by KOSEF 2006–03792.

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