

Articles

Ketene-Forming Elimination Reactions from Aryl Thienylacetates Promoted by R₂NH in MeCN. Effects of Base-Solvent and β-Aryl GroupSang Yong Pyun,* Eun Ju Cho, Hyoun Jung Seok, Ju Chang Kim, Seok Hee Lee,[†] and Bong Rae Cho^{‡,*}

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Ketene-forming eliminations from C₄H₃(S)CH₂C(O)OC₆H₃-2-X-4-NO₂ (**1**) promoted by R₂NH in MeCN have been studied kinetically. The reactions are second-order and exhibit Brønsted β=0.51-0.62 and |β_{gl}|=0.47-0.53. Hence, an E2 mechanism is evident. The Brønsted β increased from 0.33 to 0.53 and |β_{gl}| remained nearly the same by the change of the base-solvent from Bz(*i*-Pr)NH/Bz(*i*-Pr)NH₂⁺ in 70 mol% MeCN(aq) to Bz(*i*-Pr)NH-MeCN, indicating a change to a more symmetrical transition state with similar extents of C_β-H and C_α-OAr bond cleavage. When the β-aryl group was changed from thienyl to phenyl in MeCN, the β value increased from 0.53 to 0.73 and |β_{gl}| decreased from 0.53 to 0.43. This indicates that the transition state became skewed toward more C_β-H bond breaking with less C_α-OAr bond cleavage. Noteworthy is the greater double bond stabilizing ability of the thienyl group in the ketene-forming transition state.

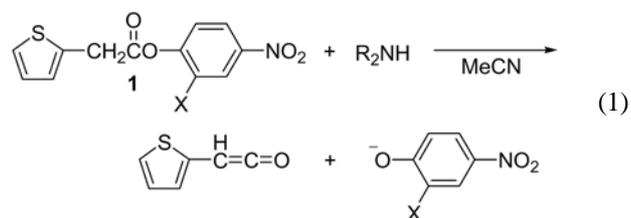
Key Words : Elimination, E2, β-Aryl group effect, Mechanism

Introduction

Base catalyzed reactions of aryl phenylacetates provide a rich mechanistic diversity ranging from hydrolysis to ketene-forming elimination reactions.¹⁻¹⁴ Whereas the former is the major reaction pathway in protic solvents with hydroxide or alkoxide as the base, the latter becomes predominant with amine bases in aprotic solvents. In protic solvents, the elimination reaction mechanism changes from E2 to E1cb as the good leaving group is made poorer and as the electron withdrawing ability of the β-aryl substituent increases. On the other hand, the E2 mechanism is the only mechanistic pathway in aprotic solvents.

Very recently, we reported the mechanism of elimination reactions of aryl thienylacetates [C₄H₃(S)CH₂C(O)OC₆H₃-2-X-4-NO₂ (**1**)] promoted by R₂NH/R₂NH₂⁺ in 70 mol% MeCN(aq).¹⁵ The reaction proceeded by the E2 mechanism when X=CF₃, NO₂. As the leaving group was made poorer (X=H, OCH₃, Cl), the E2 transition state became more skewed toward the proton transfer and the E1cb mechanism competed. In contrast, the reactions of aryl phenylacetates [PhCH₂C(O)OC₆H₃-2-X-4-NO₂ (**2**)] proceeded via an E2 mechanism under the same condition.^{14,16} The remarkable difference between the two reactions was attributed to the smaller aromatic resonance energy of thiophene than benzene.¹⁷ Because the negative charge density at the β-carbon could be delocalized by the thienyl group, the E1cb intermediate seemed to be stabilized and the E1cb mechanism competed.

While thiophene can stabilize the negative charge at the β-carbon, it can also stabilize the partial double bond character in the transition state. The double bond stabilizing ability of the thienyl group would be more pronounced in aprotic solvent where the reaction proceeds by the E2 mechanism. In order to provide an insight into the effect of base-solvent on the E2 transition state, we have investigated the reactions of aryl thienylacetates promoted by R₂NH in MeCN (eq. 1). Comparison with the existing data for the reactions of **1** with R₂NH/R₂NH₂⁺ in 70 mol% MeCN (aq) and **2** with R₂NH in MeCN reveal the effect of the base-solvent and β-aryl group on the ketene-forming eliminations.



X = H (**a**), OCH₃ (**b**), Cl (**c**), CF₃ (**d**), NO₂ (**e**)
R₂NH = Bz(*i*-Pr)NH, *i*-Bu₂NH, *i*-Pr₂NH, 2,6-DMP

Results and Discussion

Product Study. The product of reaction between **1a** and *i*-Bu₂NH in MeCN was identified by TLC and GC as before.¹⁴ The products were *N,N*-di(isobutyl)thienylamide and 4-nitrophenoxide. The yield of *N,N*-di(isobutyl)thienyl-

Table 1. Rate Constant for ketene-forming elimination from $C_4H_3(S)CH_2C(O)OC_6H_3-2-X-4-NO_2$ promoted by R_2NH in MeCN at 25.0 °C

R_2NH^b	pK_a^c	$k_2, M^{-1} s^{-1de}$				
		X = H (1a)	X = OMe (1b)	X = Cl (1c)	X = CF ₃ (1d)	X = NO ₂ (1e)
Bz(<i>i</i> -Pr)NH	16.8	0.0212	0.0172	0.673	1.93	4.73
<i>i</i> -Bu ₂ NH	18.2	0.124 ^f	0.0603	2.46	6.65	19.7
<i>i</i> -Pr ₂ NH	18.5	0.309	0.197	6.81	14.1	34.7
2,6-DMP ^f	18.9	0.390	0.317	12.6	30.3	62.0

^a[Substrate] = 8.0×10^{-5} M. ^b[R_2NH] = 2.0×10^{-3} to 5.0×10^{-2} M. ^cReference 19. ^dAverage of three or more rate constants. ^eEstimated uncertainty, $\pm 3\%$. ^f*cis*-2,6-Dimethylpiperidine.

Table 2. Brønsted β values for elimination from $C_4H_3(S)CH_2C(O)OC_6H_3-2-X-4-NO_2$ promoted by R_2NH in MeCN at 25.0 °C

	X = H (1a)	X = OMe (1b)	X = Cl (1c)	X = CF ₃ (1d)	X = NO ₂ (1e)
pK_{lg}^a	20.7	20.6	18.1	17.0	16.0
β	0.62 ± 0.05	0.59 ± 0.11	0.58 ± 0.10	0.53 ± 0.09	0.51 ± 0.04

^aReference 20.

amide determined by GC was 91%. For reactions of **1a-e** with R_2NH in MeCN, the yields of aryloxides as determined by comparing the UV absorption of the infinity sample of the kinetic runs with those of the authentic aryloxides were in the range 94-98%.

The possibility of competition by the aminolysis reaction has been ruled out as before.^{14,16} The k_2^E values for the reactions of **1a** and **1e** with 2,6-DMP in MeCN are 0.390 and $62.0 M^{-1} s^{-1}$, respectively (Table 1). The values are much larger (≥ 150 -fold) than $k_2 = 0$ and $0.292 M^{-1} s^{-1}$ reported for the aminolysis of 4-nitro- and 2,4-dinitrophenyl butyrates.¹⁴ Because steric effects of the thenyl and butyl groups are expected to be similar,¹⁸ the aminolysis of **1a** and **1e** should proceed at comparable rates to those of the former. This would predict that the ketene-forming elimination should be the predominant reaction pathway under the condition employed in this study.

Kinetic Study. The rates of elimination reactions were followed by monitoring the increase in the absorption at the

λ_{max} for the aryloxides in the range of 411-448 nm. In all cases, clean isosbestic points were noted in the range of 289-300 nm. Excellent pseudo-first-order kinetic plots which covered at least three half-lives were obtained. The plots of the k_{obs} against base concentration are 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 slopes of the plots are the overall second-order rate constants k_2 . Values of k_2 for eliminations from **1a-e** are summarized in Table 1.

Table 3. Brønsted β_{lg} values for elimination from $C_4H_3(S)CH_2C(O)OC_6H_3-2-X-4-NO_2$ promoted by R_2NH in MeCN at 25.0 °C

R_2NH	Bz(<i>i</i> -Pr)NH	<i>i</i> -Bu ₂ NH	<i>i</i> -Pr ₂ NH	2,6-DMP ^b
pK_a^a	16.8	18.2	18.5	18.9
β_{lg}	-0.53 ± 0.03	-0.51 ± 0.03	-0.47 ± 0.04	-0.50 ± 0.03

^aReference 19. ^b*cis*-2,6-Dimethylpiperidine.

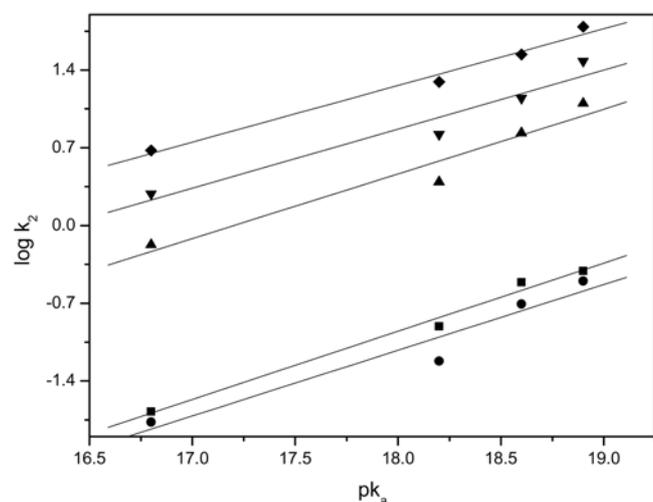
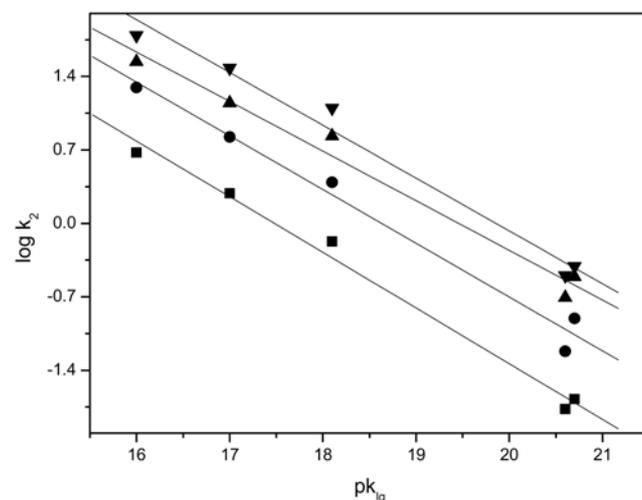
**Figure 1.** Brønsted plots for the elimination from $C_4H_3(S)CH_2C(O)OC_6H_3-2-X-4-NO_2$ promoted by R_2NH in MeCN at 25.0 °C. X = H (**1a**, ■), OMe (**1b**, ●), Cl (**1c**, ▲), CF₃ (**1d**, ▼), NO₂ (**1e**, ◆).**Figure 2.** Plots $\log k_2$ versus pK_{lg} values of the leaving group for the elimination from $C_4H_3(S)CH_2C(O)OC_6H_3-2-X-4-NO_2$ promoted by R_2NH in MeCN at 25.0 °C. R_2NH = Bz(*i*-Pr)NH (■), *i*-Bu₂NH (●), *i*-Pr₂NH (▲), 2,6-DMP (▼).

Table 4. Effect of the solvent and β -Aryl Group on the Ketene-Forming E2 Reaction of ArCH₂CO₂C₆H₃-2-CF₃-4-NO₂ Promoted by R₂NH in MeCN at 25.0 °C

	Ar = thienyl ^a	Ar = thienyl	Ar = phenyl
base-solvent	R ₂ NH/R ₂ NH ₂ ⁺ in 70 mol% MeCN(aq)	R ₂ NH-MeCN	R ₂ NH-MeCN
rel. rate (k_2^E) ^d	1.0	1.1	0.03 ^c
β	0.33 ± 0.05	0.53 ± 0.09	0.73 ± 0.05 ^c
β_g	-0.49 ± 0.04	-0.53 ± 0.03	-0.43 ^b
ΔH^\ddagger , kcal/mol	6.8 ± 0.5	4.4 ± 0.3	5.0 ± 0.6
ΔS^\ddagger , eu	-34.4 ± 2.8	-42.4 ± 1.2	-46.1 ± 1.7

^aReference 15. ^bReference 14. ^cReference 23. ^dR₂NH = Bz(*i*-Pr)NH.

Brønsted plots for eliminations from **1a-e** are depicted in Figure 1. The plots are linear with good correlations. The β values are in the range of 0.62-0.51 and decrease as the leaving group ability of the aryloxide increases (Table 2). Similarly, the elimination rates determined with different leaving groups correlated reasonably well with the leaving group pK_{lg} values (Figure 2). The β_g values are in the range 0.47-0.53 and remain nearly the same regardless of the base strength (Table 3).

Rates of elimination from **1d** promoted by Bz(*i*-Pr)NH were measured at three temperatures spanning 20 °C. Arrhenius plots exhibited excellent linearity (plots not shown). Calculated enthalpies and entropies of activation are summarized in Table 4.

Mechanism of Elimination. Results of kinetic investigations and product studies clearly establish that the reactions of **1** with R₂NH in MeCN proceed by the E2 mechanism. Because the possibility of competing aminolysis is ruled out and the ketene-forming elimination reaction 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 $|\beta_g|$.^{21,22} This conclusion is supported by the interaction coefficients. Table 2 shows that the Brønsted β values for R₂NH-promoted eliminations from **1** decrease gradually as the leaving group is made more nucleofugic. This effect corresponds to a positive p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{lg}$, which describes the interaction between the base catalyst and the leaving group.^{21,22} 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.^{21,22}

Effect of Base-Solvent. Table 4 shows the relative rates and transition state parameters for R₂NH-promoted eliminations of ArCH₂CO₂C₆H₃-2-CF₃-4-NO₂. The rate of elimination from **1** increased slightly when the base-solvent system was changed from Bz(*i*-Pr)NH/Bz(*i*-Pr)NH₂⁺ in 70 mol% MeCN(aq) to Bz(*i*-Pr)NH-MeCN. The Brønsted β increased from 0.33 to 0.53 and $|\beta_g|$ remained nearly the same by the variation of the base-solvent system, indicating that the transition state structure became more symmetrical with similar extents of C $_{\beta}$ -H and C $_{\alpha}$ -OAr bond cleavage. This result can be attributed to a solvent effect. Since the negative

charge density developed at the β -carbon and aryloxide in the transition state cannot be stabilized by solvation in MeCN, E1- or E1cb-like transition state would be destabilized and a symmetric transition state with maximum charge dispersal becomes the favored alternative. This interpretation is consistent with the smaller ΔH^\ddagger and more negative ΔS^\ddagger determined with Bz(*i*-Pr)NH-MeCN as the base-solvent system. As the partial double bond character developed in the transition state can be stabilized by resonance with the β -thienyl group, the enthalpy of activation should decrease. In addition, the entropy of activation should decrease because large solvent reorganization would be required to solvate the partial negative charge developed in the transition state with an aprotic solvent. A similar result was observed in the reactions of aryl phenylacetates under the same conditions.¹⁴

Effect of β -Aryl group. When the β -aryl group was changed from thienyl to phenyl in MeCN, the rate decreased by more than 30-fold. In addition, the β value increased from 0.53 to 0.73, and $|\beta_g|$ decreased from 0.53 to 0.43 (Table 4). This indicates that the transition state structure became more skewed toward the C $_{\beta}$ -H bond cleavage with less C $_{\alpha}$ -OAr bond cleavage by the β -aryl group variation. This is again consistent with the greater double bond stabilizing ability of the thienyl than phenyl group (*vide supra*). If the phenyl group cannot stabilize the partial double bond character by resonance as much as the thienyl group, the partial negative charge developed at the β -carbon in the transition state cannot be transferred toward the α -carbon as efficiently as in the thienyl derivative. This would predict that unsymmetrical transition state with larger C $_{\beta}$ -H bond cleavage and smaller C $_{\alpha}$ -OAr bond breaking will be more favored alternative. Consistently, the enthalpy of activation is higher due to the less partial double bond formation, while the entropy of activation is slightly more negative probably because more solvent reorganization may be necessary to solvate the more negatively charged transition state.

In conclusion, we have studied elimination reactions from **1** promoted by R₂NH-MeCN. The reactions proceed by the E2 mechanism *via* an E2-central transition. Noteworthy is the greater double bond stabilizing ability of the thienyl group in the ketene-forming transition state.

Experimental Section

Materials. Aryl thienylacetates **1** were available from previous investigations.¹⁵ Reagent grade acetonitrile and secondary amine were fractionally distilled from CaH₂.

Kinetic Studies. Reactions of **1** with R₂NH in MeCN were followed by monitoring the increase in the absorbance of the aryloxides at 411-448 nm with a UV-vis spectrophotometer as described.¹⁴⁻¹⁶

Product Studies. The products were also identified by periodically monitoring the UV absorption of the reactions mixtures under the reaction condition. For all reactions, the absorbance corresponding to the reactants decreased at 240-260 nm and those for the products increased at 411-448 nm

as the reactions proceeded. The UV spectra of the products were identified to those of the aryloxides. Clean isobestic points were observed at 289, 289, 300, 295, and 300 nm for the reaction **1a-e**, respectively. The yields of the aryloxides determined by comparing the absorbance of the infinity samples from the kinetic studies with those of the authentic aryloxides were in the range of 94-98%.

The products of reactions of **1a** with *i*-Bu₂NH in MeCN were identified by using more concentrated solutions and gas chromatographic analysis as described previously.¹⁴ The *N,N*-di(isobutyl)thenylamide was obtained in 91% yield.

Control Experiments. The stabilities of **1a-e** were determined as reported.¹⁴⁻¹⁶ Solutions of aryl thienylacetates **1a-d** were stable for at least 2 weeks in MeCN solution at room temperature. However, the solution of **1e** was stable for only 5 days.

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References

- Holomquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993-3002.
- Holomquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 3003-3006.
- Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956-5964.
- Inoue, M.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 1644-1653.
- Inoue, M.; Bruice, T. C. *J. Org. Soc.* **1982**, *47*, 959-963.
- Willian, A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 808-812.
- Willian, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 7-649.
- Tagaki, W.; Kobayashi, S.; Kurihara, K.; Kurashima, K.; Yoshida, Y.; Yano, J. *J. Chem. Soc., Chem. Commun.* **1976**, 843-845.
- Broxton, T. J.; Duddy, N. W. *J. Org. Soc.* **1981**, *46*, 1186-1191.
- Chandrasekar, R.; Venkatasubramanian, N. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1625-1631.
- Douglas, K. T.; Alborz, M.; Rullo, G. R.; Yaggi, N. F. *J. Chem. Soc., Chem. Commun.* **1982**, 242-246.
- Isaac, N. S.; Najem, T. S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 557-562.
- Chung, S. Y.; Yoh, S. D.; Choi, J. H.; Shim, K. T. *J. Korean Chem. Soc.* **1992**, *36*, 446.
- Cho, B. R.; Kim, Y. K.; Maing Yoon, C. O. *J. Am. Chem. Soc.* **1997**, *119*, 691-697.
- Cho, B. R.; Pyun, S. Y. *J. Org. Chem.* **2007**, *72*, 1198-1103.
- Cho, B. R.; Kim, Y. K.; Seong, Y. J.; Pyun, S. Y. *J. Org. Chem.* **2000**, *65*, 1239-1241.
- Bernardi, F. *J. Mol. Struct.* **1988**, *163*, 173-177.
- Charton, M. *J. Am. Chem. Soc.* **1975**, *972*, 1552-1556.
- Cho, B. R.; Lee, S. J.; Kim, Y. K. *J. Org. Chem.* **1995**, *60*, 2072-2076.
- Coetzee, J. F. *Prog. Phys. Org. Chem.* **1965**, *4*, 45-92.
- Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1987; (a) pp 214-218. (b) pp 591-616. (c) pp 640-644.
- Gandler, J. R. *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; John Wiley and Sons: Chichester, 1989; vol. 2, part 1, pp 734-797.
- Cho, B. R.; Kim, N. S.; Kim, Y. K.; Son, K. H. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1419-1423.