the chloroform, and recrystallizing the glass from acetone, which affords white crystals, mp 184-186 °C.

Acknowledgment. We thank Perry Matheny for carrying out the synthetic work and Prof. Leo Paquette for helpful discussions. A.M.M. thanks the Robert A. Welch Foundation for a fellowship, and J.P.F. thanks the National Science Foundation (NSR 84-01414) and the Welch Foundation for partial support.

Supplementary Material Available: Tables S1 and S2 listing hydrogen atomic parameters and anisotropic thermal parameters (2 pages); tables of observed and calculated structure factor amplitudes for **2b** (14 pages). Ordering information is given on any current masthead page.

Intramolecular Nucleophilic Catalysis during Alkaline Hydrolysis of Nonenolizable β-Keto Esters

William N. Washburn* and Ewell R. Cook

Contribution from the Life Sciences Division, Eastman Kodak Company, Rochester, New York 14650. *Received November 25, 1985*

Abstract: Kinetic and ^{18}O-labeling studies demonstrate that in the hydrolysis of nonenolizable acetoacetate esters, the carbonyl hydrate acts as a nucleophilic catalyst. A cyclic four-membered lactone is formed and later opens. Structure/reactivity studies showed the rate-determining step to be a function of the pK_a of the leaving group and the substituent bound to C_3 of the acetoacetate residue. Rate accelerations of 4 to 10^4 were observed for hydrolyses of the corresponding *p*-nitrophenyl esters, depending on the substituent at C_3.

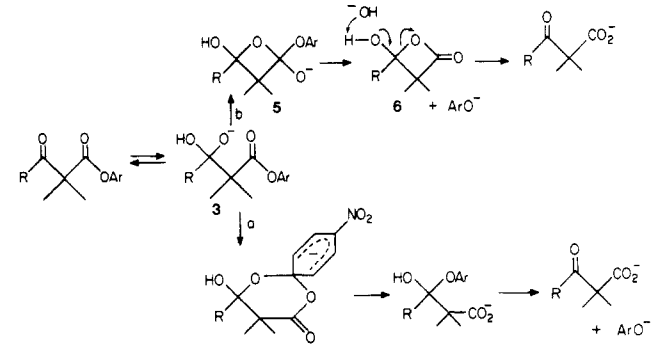
The intramolecular catalysis of alkaline hydrolysis of carboxylic esters due to a neighboring γ- or δ-hydroxyl group has been well documented.[1] Rate accelerations have also been reported for γ-keto esters since the hydrates of the carbonyls act as internal nucleophiles.[2] Hydrolytic rate enhancements of 10^4 for *o*-acetoxybenzaldehyde[2k] and 10^5 for methyl *o*-formylbenzoate[2c] have been reported. Our investigation of the hydrolysis of nonenolizable β-keto esters demonstrates that substantial acceleration arises from the β-carbonyl.

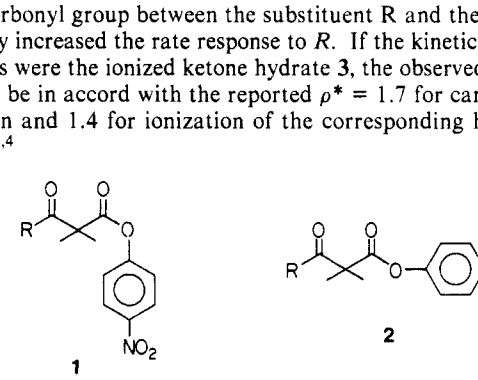
Esters **1a-g** were prepared to evaluate the effect of a β-carbonyl during hydrolysis of sterically conjested esters. The hydrolyses of **1a-g** were followed by ^1H NMR at pH 12 in 1:1 CD_3CN/H_2O. The initial hydrolysis products for each ester, except for **1g**, were *p*-nitrophenoxide and the corresponding substituted acetoacetate ion, which, depending on the substituent at C_4, decarboxylated. Alkaline hydrolysis of **1g** yielded chloroform and the half ester of *p*-nitrophenyl dimethylmalonate. By ^1H NMR, **1e** and **1f** were extensively hydrated; the ratios of hydrate to ketone were 1:3 and 3:1, respectively, in 1:1 CD_3CN/D_2O.

The hydrolysis rates of **1a-e**, measured at 400 and 290 nm, respectively, in 1:1 CH_3CN/aqueous potassium phosphate buffer (0.15 μm) over a pH range of 10-13.3, were first order in hydroxide ion. The hydrolysis rate of **1f** was first order in hydroxide ion up to pH 11 but became pH independent above pH 13, which suggests that the kinetically active species was the hydrate anion **3**, which for **1f** was almost completely formed at pH 13.

For hydrolysis of **1a-e** at pH 13.3, a plot of log *k* vs. σ^* (Figure 1) showed $\rho^* = 1.7$. Since the $\sigma^*\rho^*$ plot for the hydrolysis of *p*-nitrophenyl α-substituted isobutyrate esters under identical conditions gave $\rho^* = 0.3$, it was apparent that the insertion of the carbonyl group between the substituent R and the α-carbon greatly increased the rate response to *R*. If the kinetically active species were the ionized ketone hydrate **3**, the observed $\rho^* = 1.7$ would be in accord with the reported $\rho^* = 1.7$ for carbonyl hydration and 1.4 for ionization of the corresponding hydrate in H_2O.[3,4]

Scheme I





1

a R = CH_3
b R = CH_2OMe
c R = $CH_2OC_6H_5$
d R = CH_2Cl
e R = CHF_2
f R = CF_3
g R = CCl_3

2

a R = CH_3
b R = CH_2OMe
c R = $CH_2OC_6H_5$
d R = CH_2Cl
e R = CHF_2
f R = CF_3

In the course of elucidating the reaction mechanism, the corresponding phenyl ester series **2a-f** was prepared. The nonlinearity

(1) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(2) (a) Bhatt, M. V.; Rao, G. V.; Rao, K. S. *J. Org. Chem.* **1979**, *44*, 984. (b) Walder, J. A.; Johnson, R. S.; Klotz, I. M. *J. Am. Chem. Soc.* **1978**, *100*, 5156. (c) Bender, M. L.; Silver, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4589. (d) Bender, M. L.; Reinstein, J. A.; Silver, M. S.; Mikulak, R. *J. Am. Che. Soc.* **1965**, *87*, 4545. (e) Newman, M. S.; Hishida, S. *J. Am. Chem. Soc.* **1962**, *84*, 3582. (f) Shalitin, Y.; Bernhard, S. A. *J. Am. Chem. Soc.* **1964**, *86*, 2292. (g) Ramirez, F.; Hansen, B.; Desai, N. B. *J. Chem. Soc.* **1962**, *84*, 4588. (h) Burrows, H. D.; Topping, R. M. *J. Chem. Soc., Perkin Trans. 2* **1975**, 571. (i) Bowden, K.; Last, A. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 345. (j) Bowden, K.; Last, A. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, *351*, 358. (k) Holleck, L.; Melkonian, G. A.; Rao, S. B. *Naturwissenschaften* **1958**, *45*, 438.

(3) Greenzaid, P.; Luz, Z.; Samuel, D. *J. Am. Chem. Soc.* **1967**, *89*, 749.
(4) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1.

0002-7863/86/1508-5962$01.50/0

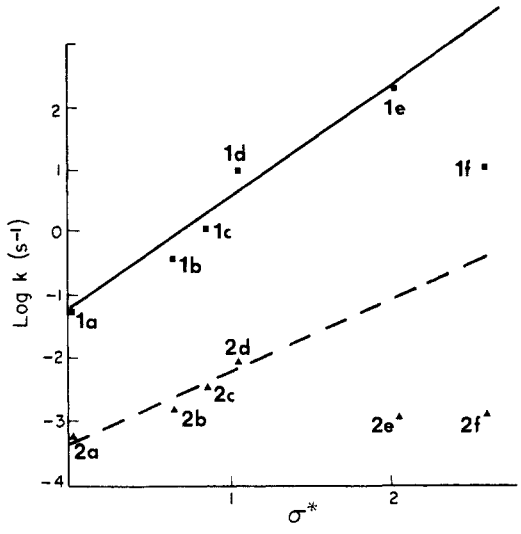


Figure 1. $\rho^* = 1.7$ ($c = 0.97$) for hydrolysis of esters **1a–e**; $\rho^* = 1.0$ ($c = 0.96$) for hydrolysis of esters **2a–d**.

of the corresponding $\sigma^*\rho^*$ plot for esters **2a–f** (Figure 1) suggested a change in rate-determining step or mechanism for the hydrolysis of these esters; $\rho^* = 1.0$ for **2a–d**. At pH 13.3, esters **1** can hydrolyze 10^2–10^5 times faster than their counterparts **2**. In contrast, *p*-nitrophenyl pivalate **7** hydrolyzed 56 times faster than phenyl pivalate **8** under these conditions. The enhanced reactivity of the *p*-nitrophenyl esters **1** relative to the phenyl esters **2** and the dependence of hydrolytic rate on substituents suggested that the ketone hydrate was providing nucleophilic catalysis.

Two possible pathways are outlined in Scheme I. Path a requires addition of the ionized hydrate to the nitrophenyl ring, thus transferring the *p*-nitrophenyl ring from the ester oxygen to an oxygen of the hydrate.[5] Path b entails the intermediacy of β-lactone **6**, which, being a pseudoacid, would ionize and ring open. The net result would be to transfer an oxygen originally bound to the ketone hydrate to the carboxylate functionality. Since both reaction pathways entail oxygen rearrangements, ^{18}O labeling would confirm if either were operative.

By mass spectral analysis, the *p*-nitrophenol hydrolysis product of ^{18}O-labeled **1e**, prepared from 66% ^{18}O-enriched *p*-nitrophenol, contained 66% ^{18}O, thereby eliminating path a from consideration. To verify path b, we prepared ^{18}O-labeled **1c** which by mass spectrometry contained 0.32 ^{18}O; from the fragmentation pattern, all of the label was at the ketone carbonyl.

The ^{18}O-labeled **1c** was partly hydrolyzed at pH 11, quenched at pH 4, and treated with excess diazomethane. The recovered **1c** contained 0.3 ^{18}O incorporated at C_3. The product, methyl 4-phenoxy-3-oxo-2,2-dimethylbutyrate (**4**), contained 0.3 ^{18}O distributed over the ketone carbonyl and the ester oxygens. From the fragmentation patterns, no more than 50% of the label was incorporated in the ester functionality. When **4** and the recovered labeled **1c** were separately exchanged as above in H_2O, all of the ^{18}O was washed out of labeled **1c**, but 0.15 ^{18}O remained in **4**. The mass spectral fragmentation pattern was consistent with 0.15 ^{18}O being distributed over the ester oxygens; no label remained at the ketone carbonyl oxygen.[6]

Only path b would account for the above ^{18}O-label distribution. The *gem*-dimethyl effect augmented by the presence of two adjacent tetrahedral centers in **3** biased the reaction course toward formation of a four-membered ring despite the >25 kcal of strain associated with intermediates **5** and **6**.

The fact that only 50% of the label was transferred to the ester functionality meant that proton exchange (making the hydrate oxygens equivalent) was faster than nucleophilic attack to form tetrahedral intermediate **5**. The observation that ester **1g** underwent exclusively the haloform reaction supported the assumption of unfavorable energetics for hydrolysis via path b. The failure of the oxygens to maintain their identities, unlike in the hydrolysis of methyl 8-benzoyl-1-naphthoate, is consistent with formation of a strained β-lactone rather than a relatively strain-free γ-lactone.[2i]

Nevertheless, despite the strained intermediates developed during the hydrolyses of esters **1a–f**, all of these compounds hydrolyzed at pH 13.3 substantially faster than **7**. For example, at pH 12.6 **1a** reacted 11 times faster than **7**, and **1e** reacted 5×10^4 faster. The rate accelerations calculated for **1a** and **1e** were ~4 and 10^4, respectively, after correction for the inductive effect of the β-carbonyl group. Thus, the extent of the nucleophilic catalysis is a function of the propensity of the β-carbonyl to form hydrate anion.

For **1a–e** the rate-limiting step is formation of intermediate **5**. However, since **1e** and **1f** hydrolyze at the same rate at pH <11, the inductive effect of the CF_3 group must stabilize the hydrate anion of **1f** sufficiently to allow reversion of **5** to **3** to compete with expulsion of *p*-nitrophenoxide to generate **6**.[7] For phenyl esters **2a–d**, since phenoxide is a poorer leaving group than *p*-nitrophenoxide, reversible formation of **5** competes with collapse of **5** to **6**; as a consequence, ρ^* diminishes. Formation of lactone **6** becomes the rate-limiting step for hydrolysis of phenyl esters **2e** and **2f**, since the inductive stabilization of the corresponding hydrate anions ensured that reversion of tetrahedral intermediate **5** to **3** would be favored over expulsion of phenoxide and concomitant formation of the more strained lactone **6**.

Although this report is the first to definitely establish the catalytic role of a β-carbonyl during ester hydrolysis, a similar reaction course was proposed to account for the facile aminolysis of β-keto esters.[9]

Experimental Section

^1H NMR spectra were obtained on a Varian EM-390 NMR spectrophotometer (90 MHz) in deuteriochloroform; the chemical shifts are reported in terms of δ and are referenced to Me_4Si. Ultraviolet–visible spectra were obtained on a Cary 14 spectrophotometer. Mass spectral data were obtained on a DuPont 21-491 or a MAT 731 spectrometer.

All chemicals employed were reagent grade or better. The substituted acetyl chlorides were commercially available except for difluoroacetyl chloride.[10]

Preparation of Esters 1a–g. Following the procedure of Brady and Smith,[11] a series of substituted acetyl chlorides were added to a EtOAc solution of dimethylketene[12] under N_2 at −75 °C. Upon removal of the solvent with an aspirator, the corresponding crude 4-substituted-3-oxo-2,2-dimethylbutyryl chlorides were converted to the corresponding *p*-nitrophenyl esters **1a–g** upon reaction with *p*-nitrophenol/triethylamine in CH_2Cl_2. The crude product was isolated by quenching the reaction with water, extraction with CH_2Cl_2, drying over $NaSO_4$, and solvent evaporation in vacuo. The desired pure esters were obtained as viscous oils after Chromatotron chromatography on silica gel with 4:1 hexane/EtOAc as the eluant. ^1H NMR: **1a** 1.54 (s, 6 H), 2.3 (s, 3 H), 7.27 (ABq, 2 H, $J = 9$ Hz), 8.28 (ABq, 2 H, $J = 9$ Hz); **1b** 1.53 (s, 6 H), 3.42 (s, 3 H), 4.2 (s, 2 H), 7.27 (ABq, 2 H), 8.28 (ABq, 2 H); **1c** 1.57 (s, 6 H), 4.72 (s, 2 H), 7.0 (m, 7 H), 8.1 (ABq, 2 H); **1d** 1.66 (s, 6 H), 4.3 (s, 2 H), 7.2 (ABq, 2 H), 8.1 (ABq, 2 H); **1e** 1.63 (s, 6 H), 6.06 (t, 1 H, $J = 52$ Hz), 7.24 (ABq, 2 H), 8.2 (ABq, 2 H); **1f** 1.65 (s, 6 H), 7.24 (ABq, 2 H), 8.28 (ABq, 2 H); **1g** 1.8 (s, 6 H), 7.35 (ABq, 2 H), 8.33 (ABq, 2 H).

Preparation of Esters 2a–f. In an analogous procedure, phenyl esters **2a–f** were prepared and purified. ^1H NMR: **2a** 1.48 (s, 6 H), 2.27 (s, 3 H), 7.0 (m, 2 H), 7.3 (m, 3 H); **2b** 1.5 (s, 6 H), 3.4 (s, 3 H), 4.2 (s, 2 H), 7.07 (m, 2 H), 7.3 (m, 3 H); **2c** 1.57 (s, 6 H), 4.72 (s, 2 H), 7.1 (m, 10 H); **2d** 1.53 (s, 6 H), 4.3 (2 H), 7.1 (m, 2 H), 7.27 (m, 3 H); **2e** 1.57 (s, 6 H), 5.98 (s, 1 H, $J = 52$ Hz), 7.0 (m, 2 H), 7.27 (m, 3 H); **2f** 1.6 (s, 6 H), 7.3 (m, 5 H).

(5) For a recent example of a *p*-nitrophenyl ester undergoing a facile Smiles rearrangement, see: Fitzgerald, L. R.; Blakeley, R. L.; Zerner, B. *Chem. Lett.* **1984**, 29.

(6) Labeled **1c** was completely hydrolyzed with potassium phosphate buffer at pH 12 and partially hydrolyzed in the absence of a buffer. In both cases less than 50% of the ^{18}O label was transferred to the carboxylate group.

(7) The addition of alkoxides or hydroxide to normal phenolic esters is normally irreversible, resulting in the release of the phenoxide.[8]

(8) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626.

(9) Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* **1985**, 105.

(10) Prober, M. *J. Am. Chem. Soc.* **1953**, *75*, 968.

(11) Brady, W. T.; Smith, L. *J. Chem. Soc. C* **1970**, 2522.

(12) Smith, C. W.; Norton, D. G. *Org. Synth.* **1924**, *4*, 348.

Kinetics. The hydrolytic rate constants were measured in degassed 1:1 CH_3CN/H_2O containing 0.025 M potassium phosphate. The increase in OD at 400 nm was monitored for 10^{-4} M solutions of the *p*-nitrophenyl esters **1** with a Cary 14 spectrophotometer; for 10^{-3} M solutions of phenyl esters **2**, the increase at 290 nm was monitored. Pseudo-first-order rate constants, cited below, were obtained from a least-squares analysis of the data.

The kinetic data are given in the format substrate: rate constant in s^{-1} (pH). **1a**: 3.1×10^{-2} (13.1), 4.1×10^{-3} (12.3); **1b**: 4.9×10^{-2} (12.6), 6.9×10^{-3} (11.7); **1c**: 2.2×10^{-2} (11.4), 7.3×10^{-3} (10.8); **1d**: 0.13 (11.6), 2.4×10^{-3} (10.0); **1e**: 47 (12.76), 12.2 (11.85), 0.79 (10.65); **1f**: 7.1 (12.8), 3.8 (11.9), 1.1 (11.0); **2a**: 6.5×10^{-4} (13.3); **2b**: 1.8×10^{-3} (13.4), 8.9×10^{-4} (13.0); **2c**: 2.5×10^{-3} (13.15), 5.0×10^{-4} (12.5); **2d**: 1.4×10^{-2} (13.4), 6.8×10^{-3} (13.0), 1.3×10^{-3} (12.4); **2e**: 1.0×10^{-3} (13.4), 4.5×10^{-4} (12.8); **2f**: 1.25×10^{-3} (13.2), 2.4×10^{-4} (12.5); **7**: 1.14×10^{-2} (13.3); **8**: 2.05×10^{-4} (13.3).

Hydrolysis of ^{18}O-Labeled 1c. A solution of 40 mg of **1c** in 1 mL of dry THF, containing 40 μL of 98% ^{18}O-enriched H_2O and one drop of trifluoroacetic acid, stood for 10 h at 25 °C. After removing the volatiles by mass spectrometry, the recovered **1c** contained 32% ^{18}O at C_3.

A solution of 20 mg of labeled **1c** in 2 mL of 1:1 CH_3CN/aqueous potassium phosphate buffer at pH 11 was stirred for 5 min, quenched with KH_2PO_4, and extracted with EtOAc. The crude extract was treated with a large excess of CH_2N_2 in Et_2O for 10 min and stripped to dryness to yield a 1:3 mixture of **4** and **1c**. (Methylation was required to prevent decarboxylation during mass spectral analysis.) Filtration of the crude residue through a silica gel pad with CH_2Cl_2 eluted a mixture of recovered labeled **1c** and **4**. The mixture was resolved by preparative thin-liquid chromatography (TLC) on silica gel with CH_2Cl_2. (The extent of exchange of the ^{18}O label from the ketone carbonyl was a function of how long the compound was on the TLC plate.) **4**: NMR 1.43 (s, 6 H), 3.68 (s, 3 H), 4.7 (s, 2 H), 6.9 (m, 3 H), 7.23 (m, 2 H).

Analysis of ^{18}O Distribution. Esters **4** and **1c**, upon electron impact in the mass spectrometer, generate the following set of ions: M^+, M - OR, M - CO_2R, M - OC_6H_5. The ^{18}O enrichment for each ion can be determined by comparison of the above peaks to their counterparts two mass units higher after correction for the natural isotopic distribution. The data are given in the format substrate, MS ion (% ^{18}O incorporation). Labeled **1c** prior to hydrolysis: M^+ (32), M - OC_6H_5 (32), M - CO_2Ar (32); **1c** recovered after partial hydrolysis prior to preparative TLC: M^+ (29), M - OC_6H_5 (30); **1c** recovered after H_3O^+ exchange: M^+ (0); **4** prior to preparative TLC: M^+ (30), M - OC_6H_5 (30); **4** after preparative TLC: M^+ (18), M - CO_2Me (8), M - OC_6H_5 (20); **4** after H_3O^+ exchange: M^+ (15), M - CO_2Me (0), M - OC_6H_5 (15).

Acknowledgment. We thank Joe Wright for the ^{18}O mass spectral analyses and Prof. William Jencks for many helpful discussions.

Registry No. 1a, 103439-27-6; **1b**, 103439-28-7; **1c**, 103439-29-8; **1c**-^{18}O, 103439-40-3; **1d**, 103439-30-1; **1e**, 103439-31-2; **1e**-^{18}O, 103439-42-5; **1f**, 103439-32-3; **1g**, 103439-33-4; **2a**, 103439-34-5; **2b**, 103439-35-6; **2c**, 103439-36-7; **2d**, 103439-37-8; **2e**, 103439-38-9; **2f**, 103439-39-0; **4**, 103439-41-4; $CH_3C(O)Cl$, 75-36-5; $CH_3OCH_2C(O)Cl$, 38870-89-2; $PhOCH_2C(O)Cl$, 701-99-5; $CH_2ClC(O)Cl$, 79-04-9; $CHF_2C(O)Cl$, 381-72-6; $CF_3C(O)Cl$, 354-32-5; $CCl_3C(O)Cl$, 76-02-8; $CH_3C(O)C(CH_3)_2C(O)Cl$, 30274-05-6; $CH_3OCH_2C(O)C(CH_3)_2C(O)Cl$, 103439-23-2; $PhOCH_2C(O)C(CH_3)_2C(O)Cl$, 103439-24-3; $CH_2ClC(O)C(CH_3)_2C(O)Cl$, 30274-02-3; $CHF_2C(O)C(CH_3)_2C(O)Cl$, 103439-25-4; $CF_3C(O)C(CH_3)_2C(O)Cl$, 103439-26-5; $CCl_3C(O)C(CH_3)_2C(O)Cl$, 17953-83-2; *p*-$NO_2C_6H_4OH$, 100-02-7; *p*-$NO_2C_6H_4{}^{18}OH$, 20168-37-0; PhOH, 108-95-2; dimethylketene, 598-26-5.

Lewis Acid Catalysis of Photochemical Reactions. 6. Selective Isomerization of β-Furylacrylic and Urocanic Esters

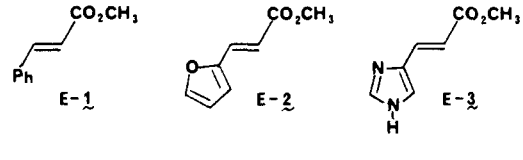
Frederick D. Lewis,* Daniel K. Howard, Joe D. Oxman, Alana L. Upthagrove, and Suzanne L. Quillen

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received January 22, 1986*

Abstract: The spectroscopic properties and thermal and photochemical isomerization reactions of (*E*)- and (*Z*)-β-furylacrylic and urocanic esters in the presence and absence of Lewis acids have been investigated. As is the case for cinnamic esters, complexation of β-furacrylic esters occurs on the carbonyl oxygen and results in a large red shift in the electronic absorption spectra and photostationary states enriched in the thermodynamically less stable *Z* isomer. Unlike cinnamic and β-furlacrylic esters, the *Z* isomer of methyl urocanate is more stable than the *E* isomer due to the formation of a moderately strong intramolecular hydrogen bond from the imidazole N_1-H to the carbonyl oxygen. Complexation of both *E*- and *Z*-methyl urocanate with BF_3 occurs on the imidazole N_3 rather than carbonyl oxygen and causes a large blue-shift in their electronic absorption spectra. The free esters undergo reversible *E*,*Z* photoisomerization whereas their BF_3 complexes undergo one-way $E \rightarrow Z$ photoisomerization. The failure of the complexed (*Z*)-urocanate to photoisomerize is attributed to an increase in the intramolecular hydrogen bond strength upon complexation.

We have recently reported that irradiation of α,β-unsaturated esters in the presence of Lewis acids such as BF_3 or $EtAlCl_2$ can result in enhanced $E \rightarrow Z$ photoisomerization and inhibition of competing unimolecular photochemical processes.[1-3] For example, 313-nm irradiation of methyl (*E*)-cinnamate (*E*-**1**) in the absence or presence of 0.2 mol equiv of $EtAlCl_2$ results in optimum yields of 46% and 92% *Z*-**1**, respectively.[1,2] Enhanced $E \rightarrow Z$ isomerization results from selective excitation of the ground-state complex of the Lewis acid with the ester carbonyl oxygen.

We report here the results of our investigation of photoisomerization reactions of two heterocyclic analogues of methyl cinnamate, methyl furylacrylate (3-(2-furyl)propenoate, **2**), and methyl urocanate (3-(1-*H*-imidazol-4-yl)propenoate, **3**). The photoisomerization reactions of *E*-**3**[4,5] and of the parent acids of



(1) Lewis, F. D.; Oxman, J. D.; Gibson, L. L.; Hampsch, H. L.; Quillen, S. L. *J. Am. Chem. Soc.* **1986**, *10*, 3005.
(2) Lewis, F. D.; Oxman, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 7345.
(3) Lewis, F. D.; Howard, D. K.; Barancyk, S. V.; Oxman, J. D. *J. Am. Chem. Soc.* **1986**, *108*, 3016.

0002-7863/86/1508-5964$01.50/0