Intramolecular Imidazole-Promoted General-Base Catalysis of the Hydrolysis of an Acetylimidazole

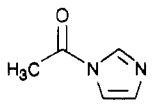
R. S. Brown* and R. G. Clewley

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

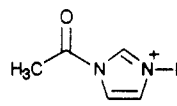
Received October 15, 1986

Intramolecular general-base catalysis of the hydrolysis of an acetylimidazole by imidazole is assessed by studying the hydrolysis of 2-(imidazol-2-ylmethyl)-*N*-acetylimidazole (**3**). The pH vs. log k_{obsd} profile exhibits three major domains that consist of H_2O attack on the protonated acetylimidazolium unit, OH^- attack on the neutral material, and an intramolecular general-base catalysis of H_2O on the neutral species. Consistent with the latter is a plateau observed in the pH profile ($k_3 = 1.02 \times 10^{-3}$ s^{-1}) at neutrality and a solvent kinetic isotope effect of $k_{H_2O}/k_{D_2O} = 2.8$ in that region. The effective molarity of the intramolecular imidazole in **3** can be assessed by comparing the value of k_3 with the second-order rate constant for 2-methylimidazole catalyzing the hydrolysis of 2-methyl-*N*-acetylimidazole (**4**). After the difference in the imidazole pK_a values is corrected for, the effective molarity of the intramolecular catalyst is 3 M.

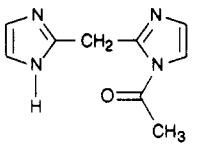
The acyl-transfer and hydrolysis reactions of acetylimidazole (**1**) and acetylimidazolium (**2**) have been extensively studied.[1] Early studies by Jencks and Carriulo[1a]



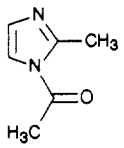
1



2: R = H, CH_3



3



4

indicated imidazole buffers accelerated the hydrolysis of **1**. Because of the symmetry of the nucleophilic reaction, the acceleration was due to general catalysis. Subsequently, it was shown that the imidazolium ion catalyzed the attack of strongly basic amines on **1** (general-acid catalysis) while the attack of weakly basic amines was subject to general-base catalysis by imidazole.[1d]

Intramolecular general catalysis of hydrolysis of esters[2] and thio esters[3] by imidazole has been observed in a number of studies. Herein we report the hydrolytic pH profile of a special amide, **3**, which allows an assessment of the efficiency of intramolecular imidazole general catalysis of the hydrolysis of an acetylimidazole without the kinetic importance of intramolecular nucleophilic acyl transfer. The latter process, if it occurs, leads to the same material and cannot contribute to its hydrolysis.

Experimental Section

N-Acetyl-2-methylimidazole (**4**) was prepared according to a published procedure.[4] Diimidazol-2-ylmethane (**5**) was prepared by an adaptation of the procedure of Joseph et al.[5] from diethyl iminomalonate dihydrochloride. The latter material, in our hands, was not obtainable by the reported routes[6] but was prepared in crude form as follows.

A solution of 13.2 g (0.2 mol) of malononitrile in 500 mL of dry dioxane was added over a 12-h period to a stirred solution of 24.5 mL of dry ethanol in 500 mL of dioxane held at 0 °C and through which a continuous stream of HCl gas was bubbled. The mixture was stirred an additional 1 h and then filtered. The white powder was washed with dry ether and allowed to dry in a desiccator under reduced pressure: yield 22.6 g; mp 109 °C (lit.[6a] mp 119–120 °C; lit.[6b] mp 134–135 °C). A second crop was obtained from the filtrate on standing: yield 12.6 g; mp 96–98 °C. (The major impurities appeared to be ammonium chloride and malononitrile polymers, but these did not affect the subsequent reactions.)

To a stirred solution of 40.0 g (0.3 mol) of aminoacetaldehyde diethyl acetal (Aldrich) in 180 mL of ethanol was added 30.0 g of crude diethyl iminomalonate dihydrochloride in portions over a 30-min period, taking care that the reaction mixture temperature did not exceed 15 °C. After it was stirred 1 h, the mixture was filtered and the white solid obtained was washed with ethanol, followed by ether. The yield of N^1,N^3-bis(2,2-diethoxyethyl)-malonodiamidine dihydrochloride was 42.7 g (35% based on aminoacetaldehyde diethyl acetal): mp 170 °C (sharp); ^{1}H NMR (Me_2SO-d_6) δ 4.64 (t, 2 H, J = 5 Hz), 4.10 (s, 2 H), 3.54 (d, 4 H, J = 5 Hz), 3.47 (q, 4 H, J = 7 Hz), 1.05 (t, 12 H, J = 7 Hz). Anal. Calcd for $C_{15}H_{34}Cl_2N_4O_4$: C, 44.45; H, 8.45; Cl, 17.49; N, 13.82. Found: C, 44.09; H, 8.51; Cl, 17.45; N, 14.00.

A solution of 41.5 g (0.1 mol) of the above malonodiamidine dihydrochloride salt in 6.0 mL of concentrated HCl was heated on a steam bath for 2 h. After cooling to ambient temperature, the dark mixture was neutralized with NH_4OH, and an amorphous mass formed. This was redissolved in H_2O and the resulting solution, along with the mother liquor, made strongly alkaline with NaOH. The water was evaporated and the remaining solid continuously extracted (Soxhlet) with 95% CH_2Cl_2/5% ethanol. A total of 10.6 g of a brown solid (crude yield 71%) was obtained. Recrystallization from methanol gave off-white crystals of diimidazol-2-ylmethane (**5**): mp 235 °C dec (lit.[5] mp 235 °C); ^{1}H NMR (Me_2SO-d_6) δ 6.89 (s, 4 H), 4.03 (s, 2 H).

2-(Imidazol-2-ylmethyl)-*N*-acetylimidazole (**3**) could not be separately prepared as a stable material but was obtained in situ

(1) (a) Jencks, W. P.; Carriulo, J. *J. Biol. Chem.* **1959**, *234*, 1272, 1280. (b) Wolfenden, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 4390. (c) Oakenfull, D. G.; Jencks, W. P. *Ibid.* **1971**, *93*, 178. (d) Oakenfull, D. G.; Salvensen, K.; Jencks, W. P. *Ibid.* **1971**, *93*, 188. (e) Palaitis, W.; Thornton, E. R. *Ibid.* **1975**, *97*, 1193. (f) Klinman, J. P.; Thornton, E. R. *Ibid.* **1968**, *90*, 4390. (g) Huskey, W. P.; Hogg, J. L. *J. Org. Chem.* **1981**, *46*, 43. (h) Hogg, J. L.; Phillips, M. K. *Tetrahedron Lett.* **1977**, *30*, 11. (i) Hogg, J. L.; Phillips, M. K.; Jergens, D. E. *J. Org. Chem.* **1977**, *42*, 2459. (j) Page, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 8818, 8828. (k) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* 1986, *108*, 4631 and references therein.

(2) (a) Komiyama, M.; Roesel, T. R.; Bender, M. L. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 23. (b) Mallick, I. M.; D'Souza, V. T.; Yamaguchi, M.; Lee, J.; Chalabi, P.; Gadwood, R. C.; Bender, M. L. *J. Am. Chem. Soc.* **1984**, *106*, 7252. (c) Felton, S. M.; Bruice, T. C. *Ibid.* **1969**, *91*, 6721. (d) Boudreau, J. A.; Farrar, C. R.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 46. (e) Utaka, M.; Koyama, J.-I.; Takeda, A. *J. Am. Chem. Soc.* **1976**, *98*, 984. (f) Utaka, M.; Takatsu, M.; Takeda, A. *Bull, Chem. Soc. Jpn.* **1977**, *50*, 3276. (g) Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 2463. (h) Williams, A.; Salvadori, G. *J. Chem. Soc. B* **1971**, 2401.

(3) (a) Street, J. P.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 6084. (b) Street, J. P.; Skorey, K. I.; Brown, R. S.; Ball, R. G. *Ibid.* **1985**, *107*, 7669.

(4) Reddy, G. S.; Mandell, L.; Goldstein, J. H. *J. Chem. Soc.* **1963**, 1414.

(5) Joseph, M.; Leigh, T.; Swain, M. L. *Synthesis* **1977**, 459.

(6) (a) McElvain, S. M.; Schroede, J. P. *J. Am. Chem. Soc.* **1949**, *71*, 40. (b) Kenner, G. W.; Lythgoe, B.; Todd, A. R. *J. Chem. Soc.* **1943**, 574.

0022-3263/87/1952-1216$01.50/0

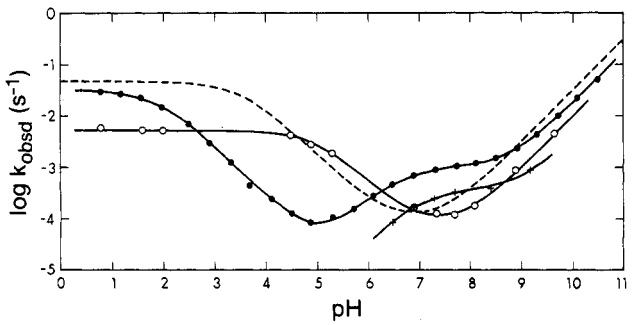


Figure 1. log k_{obsd} vs. pH data for the hydrolysis of **3** (●) and **4** (○) in H_2O at 25 °C, μ = 0.5 M $NaClO_4$, and for **3** in D_2O (+). Dotted line represents the literature profile for acetylimidazole.[1a]

by the equilibration of the N,N′-diacetylated material (**6**) and excess **5**. The diacetylated material was obtained in 91% yield as follows. To 0.75 g (5 mmol) of **5** was added 7.5 mL of acetic anhydride. The mixture was stirred for 5 min, and then 150 mL of dry ether was added. A tan powder precipitated: mp 150 °C dec; ^1H NMR [$(CD_3)_2SO$] δ 7.70 (d, 2 H, J = 2 Hz), 6.83 (d, 2 H, J = 2 Hz), 4.55 (s, 2 H), 2.56 (s, 6 H). Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.77; H, 5.33; N, 24.13. A solution of 30 mg of **5** and 3 mg of **6** in 1.0 mL of $(CD_3)_2SO$ after 30 min at 100 °C gave a mixture of 13% **3** and 87% **5** (by ^1H NMR). Compound **3**: ^1H NMR [$(CD_3)_2SO$] δ 7.70 (d, 1 H, J = 2 Hz), 6.89 (apparent s, 3 H), 4.34 (s, 2 H), 2.56 (s, 3 H).

Rates of hydrolysis of **3** and **4** were monitored at 25.0 ± 0.2 °C with a Hewlett-Packard 8451 spectrophotometer by observing the decrease in absorbance at 260 and 255 nm, respectively. Buffers were formulated in the range 0.02–0.4 M from commercially available materials: pH 0.8–2.0, $HClO_4$; pH 2.5–2.9, chloroacetic acid; pH 3.3–3.7, formic acid; pH 4.1–5.3, acetic acid; pH 5.7–6.5 and pD 6.5–6.9, MES [2-(*N*-morpholino)ethanesulfonic acid]; pH 6.9–7.7 and pD 7.3–7.7, MOPS [3-(*N*-morpholino)-propanesulfonic acid]; pH 6.9–8.1, 2-methylimidazole; pH 8.1–8.5 and pD 8.4, Tricine [*N*,*N*,*N*-tris(2-hydroxyethyl)glycine]; pH 8.9–9.7 and pD 9.2, CHES [(cyclohexylamino)ethanesulfonic acid]; pH 10.1–10.5, CAPS [(cyclohexylamino)propanesulfonic acid]. Ionic strength was maintained throughout at 0.4 M by the addition of an appropriate amount of $NaClO_4$ or, in the case of the 2-methylimidazole buffers and the buffered D_2O solutions, KCl. pH readings were made with a Radiometer TTT-2 titrator module using a Radiometer GK 2321C combination electrode standardized with Fisher certified buffers (pH 4.00, 7.00, 10.00) immediately before use. For the D_2O experiments, pD was determined by the formula pD = meter pH reading + 0.4.

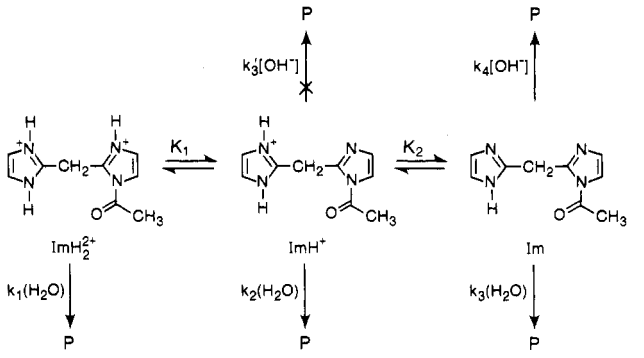
Reactions were initiated by injecting 7.5–40 μL of a stock solution of **3** or **4** in Me_2SO into 3.0 mL of buffer held in 1-cm quartz cuvettes. The stock solution from the hydrolysis studies of **3** consisted of 3 mg of **6** and 30 mg of **5** in 1.0 mL of Me_2SO equilibrated as above. Varying the volume of stock solution injected did not affect the rate, indicating that the excess **5** present did not influence the kinetics. pH was monitored immediately following a kinetic run; the variation did not exceed 0.03 pH unit.

Pseudo-first-order rate constants (k_{obsd}) for the hydrolysis of **3** and **4** were evaluated by fitting the absorbance vs. time data to a standard exponential model ($A_t = A_\infty + (A_{t0} - A_\infty)e^{-kt}$) by a nonlinear least-squares treatment. Values reported in the supplementary material (Tables S1 and S2) are averages of duplicate or triplicate measurements. In all cases, the reactions were followed to at least 80% completion and displayed excellent pseudo-first-order kinetics. Provided as supplementary material are the rate constants for hydrolysis of **3** in H_2O (D_2O) (Table S1) and **4** (Table S2).

Results and Discussion

Shown in Figure 1 is the log k_{obsd}/pH profile for the hydrolysis of **3**. Catalysis was observed with formate, chloroacetate, acetate, and tricene buffers, and the illustrated points are extrapolated to [buffer] = 0. Also shown in the figure for comparison purposes is the reported profile for acetylimidazole (**1**)[1a] and the partial profile for

Scheme I



2-methylacetylimidazole (**4**) determined in this study as well as the plateau region for **3** in D_2O.

The shape of the curve suggests three pH-dependent forms of **1** are hydrolytically important. On the basis of the process illustrated in Scheme I, the expression relating k_{obsd} to [H^+] is given in eq 1. Nonlinear least-squares

$$k_{obsd} = \frac{k_1[H^+]^3 + k_2K_1[H^+]^2 + k_3K_1K_2[H^+] + k_4K_wK_1K_2}{[H^+]^3 + K_1[H^+]^2 + K_1K_2[H^+]} \quad (1)$$

fitting of the data (Table S1, supplementary material) to eq 1 gives the following parameters: $k_1 = 3.21 \times 10^{-2}$ s^{-1}; $k_2 = 3.09 \times 10^{-5}$ s^{-1}; $k_3 = 1.02 \times 10^{-3}$ s^{-1}; $k_4 = 1.69 \times 10^2$ M^{-1} s^{-1}; pK_1 = 1.93; pK_2 = 6.60. The calculated pH dependence is shown as the solid line in Figure 1, which fits the data well.

The profile for **4** is typical for that of an acetylimidazole.[1] The various constants defined in eq 2 are as follows: $k_{H^+}(4) = 5.38 \times 10^{-3}$ s^{-1}; p$K_a(4)$ = 5.03; $k_{H_2O}(4) = 7.10 \times 10^{-5}$ s^{-1}; $k_{OH^-}(4) = 97.6$ M^{-1} s^{-1}.

$$P \xleftarrow{k_{H^+}(4)\,(H_2O)} 4\text{-}H^+ \overset{K_a(4)}{\rightleftharpoons} 4 \xrightarrow[k_{H_2O}(4)]{k_{OH^-}(4)} P \quad (2)$$

A couple of points are of note in the hydrolysis of **3**. The inclusion of the term representing H_2O attack on Im-H^+ (k_2, Scheme I) seems justified by the fact that the fits are better than if such is omitted. That rate constant (3.09×10^{-5} s^{-1}) is smaller than an analogous one for H_2O attack on acetylimidazole (8.3×10^{-5} s^{-1}),[1a] presumably due to steric buttressing in the transition state for the former process.

The main region of import for our purposes is the plateau observed around neutrality. This is ascribable to an intramolecular general-base-assisted attack of H_2O on Im (k_3, Scheme I) or a kinetically equivalent intramolecular general-acid-catalyzed attack of OH^- on Im-H^+.[7] We believe the latter can be ruled out by the following rationale.

The molecule for comparison purposes with no covalently attached imidazole unit is **4**. The rate constants for H_2O and OH^- attack on **4** are 7.10×10^{-5} s^{-1} and 97.6 M^{-1} s^{-1}, respectively, the latter value comparing favorably with the attack of OH^- on **1** (k_4 Scheme I). For the kinetically equivalent process (OH^- on Im-H^+),[7] nonlinear least-squares fitting of the data yields $k_3' = 2.55 \times 10^4$ M^{-1} s^{-1}, which requires that the imidazolium ion in ImH^+ catalyze the attack of the strong nucleophile (OH^-) by 100-fold relative to its attack on **4** or Im. It is reasonable to expect that such acceleration should also be evident for a weaker

(7) For that process, the third term in the numerator for eq 1 is replaced by $k_3K_wK_1[H^+]$, the terms representing the processes indicated in Scheme I.

nucleophile (H_2O). However, we see that k_2 (Scheme I) is actually less than the rate constant for the attack of H_2O on 4 (or 1), perhaps as a consequence of a larger steric encumbrance of the transition state. Hence, the more likely origin of the plateau region of Figure 1 stems from an intramolecular general-base role for the imidazole in Im. Consistent with this is the observed kinetic solvent isotope effect of $k_{H_2O}/k_{D_2O} = 2.8$ in the plateau region. Similar solvent isotope effects are observed in other intramolecular imidazole general-base-assisted hydrolytic processes.[2,3]

The efficacy of the intramolecular imidazole catalyst can be assessed by determining its "effective molarity".[8] This was determined by assessing the intermolecular general-base catalysis effected by 2-methylimidazole buffers on the hydrolysis of 4. As in the imidazole-catalyzed hydrolysis of other acylimidazoles,[1] the buffer acts as both a general-acid and general-base catalyst. The respective values of 5.6×10^{-5} and 1.13×10^{-3} M^{-1} s^{-1} are obtained from the plots of the second-order catalytic constant against percent free base. The pK_a for 2-methylimidazole is 7.59[9a,b] while the Brønsted β value for general-base catalysis of the hydrolysis of acetylimidazole is 0.55.[1c] If that β value also obtains for 4 then an intermolecular general base of pK_a 6.60 (pK_2 in Scheme I) possesses a catalytic constant of $\sim 3.3 \times 10^{-4}$ M^{-1} s^{-1}. Thus, the effective molarity of the intramolecular imidazole in 3 is 1.02×10^{-3} $s^{-1}/3.3 \times 10^{-4}$ M^{-1} s^{-1} = 3.1 M, consistent with the normal range observed in the hydrolysis of esters.[8]

Acknowledgment. We gratefully acknowledge the financial assistance of the U.S. Army Medical Research and Development Command (Contract No. DAMD17-85C-5173), the University of Alberta, and the Natural Sciences and Engineering Research Council of Canada (UV instrumentation grant).

Supplementary Material Available: Tables S1 and S2, giving hydrolytic rate constants for 3 and 4 (3 pages). Ordering information is given on any current masthead page.

(8) (a) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183. (b) Kirby, A. J. *Stud. Org. Chem. (Amsterdam)* **1981**, *10*, 219.

(9) (a) The pK_a of 2-methylimidazole at 7.85 at μ = 0.04–0.11 M is reported in: Perrin, D. D. In *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965. (b) pK_a = 7.59, μ = 0.3 M: Skorey, K. I. unpublished observation.

Synthesis and Photochemistry of 1-Diazo-2-cyclopentene and 2-Diazobicyclo[3.2.0]hepta-3,6-diene

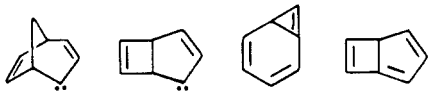
Orville L. Chapman* and Christopher J. Abelt

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Received November 22, 1983

A potentially general route to cyclic α,β-unsaturated diazo compounds via enone tosylhydrazones is described. The unsaturated tosylhydrazone is generated by sulfoxide elimination. Syntheses of 2-diazobicyclo[3.2.0]hepta-3,6-diene and 1-diazo-2-cyclopentene are reported. Photolysis of 2-diazobicyclo[3.2.0]hepta-3,6-diene in an argon matrix at 10 K gives cycloheptatetraene, and similar irradiation of 1-diazo-2-cyclopentene gives cyclopentadiene.

Vinyl carbenes continue to be a rich source of interesting chemistry.[1] Murahashi[2] has found that bicyclo[3.2.1]-octa-2,6-dien-4-ylidene (1) rearranges to styrene. We were intrigued in that styrene is also produced in the pyrolysis of tolyldiazomethanes by way of tolylmethylene–methylcycloheptatetraene interconversions.[3] We sought to investigate the lower homologue, bicyclo[3.2.0]hepta-2,6-dien-4-ylidene (2), to examine its possible role in the phenylmethylene–cycloheptatetraene and related interconversions on the C_7H_6 energy surface.[4] If Murahashi's mechanism operates in this system, then bicyclo[4.1.0]-hepta-2,4,6-triene (3) ought to be produced. 2 also offers a potential route into triene 4 either by a C–H insertion or by a 1,2-shift of the 1,5-bond. Triene 4 is thought to be a critical intermediate in the high-temperature ring contraction of phenylmethylene to fulveneallene and cyclopentadienylacetylene.[5] Finally, 2 has been implicated in the pyrolysis of norbornadienyl acetate.[6]



1 2 3 4

The generation of 2 is accomplished by photolysis of the corresponding diazo compound which, in turn, is generated from pyrolysis of the corresponding tosylhydrazone sodium salt. Tosylhydrazones are routinely prepared by reaction of tosylhydrazine with ketones or aldehydes. This simple reaction fails with enone 5 because tosylhydrazine first adds in a Michael fashion. 1,4-Addition has been observed with other reactive enones such as 2-cyclopentenone.[7] This paper describes a convenient preparation for the

(1) Hartzler, H. D. In "Carbenes"; Moss, R. A.; Jones, M., Jr., Eds.; Robert E. Krieger: Malabar, Florida, 1973; Vol. 2, pp 57–73.
(2) Murahashi, S.-I.; Okumura, K.; Naota, T.; Nagase, S. *J. Am. Chem. Soc.* **1982**, *104*, 2466–2475. Freeman, P. K.; Swenson, K. E. *J. Org. Chem.* **1982**, *47*, 2033–2039.
(3) Chapman, O. L.; McMahon, R. J.; West, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 7973–7974. Chapman, O. L.; Tsou, U.-P. E. *J. Am. Chem. Soc.* **1984**, *106*, 7974–7976.
(4) West, P. R.; Chapman, O. L.; LeRoux, J.-P. *J. Am. Chem. Soc.* **1982**, *104*, 1779–1782. McMahon, R. J.; Abelt, C. J.; Chapman, O. L.; Johnson, J. W.; Kreil, C. L.; LeRoux, J.-P.; Mooring, A. M.; West, P. R. *J. Am. Chem. Soc.*, in press.
(5) Wentrup, C. In "Reactive Intermediates"; Abramovitch, R. A., Ed.; Plenum Press: New York, 1980; Vol. 1, pp 263–297.
(6) Hoffman, R. W.; Loof, I. H.; Wentrup, C. *Justus Liebigs Ann. Chem.* **1980**, 1198–1206.
(7) Kirmse, W.; Ruetz, L. *Justus Liebigs Ann. Chem.* **1969**, *726*, 30–35. Royals, E. E. "Advanced Organic Chemistry"; Prentice-Hall: New York, 1954; p 668.

0022-3263/87/1952-1218$01.50/0