Dienone Intermediates in the Pummerer Rearrangement of 4-Methylsulfinyl-3,5-xylenol

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The rearrangement of sulfoxides to α-substituted derivatives of the corresponding sulfides is well documented[1,2] and is widely known as the Pummerer reaction. The number of interesting variations on this reaction reported recently[3] suggests that its synthetic utility has been relatively underdeveloped.

We have previously described[4] (for gas–liquid chromatography characterization purposes) the rapid transformation of 4-methylsulfinyl-3,5-xylenol (1) to the bis(trifluoroacetyl)catechol analogue **2** after reaction with trifluoroacetic anhydride at room temperature. Mechanistically it was inferred that upon initial trifluoroacetylation of the sulfoxide oxygen, the trifluoroacyl anion removed a proton from the phenolic OH moiety rather than from the S–CH_3 group. This could result in production of the intermediate 2,4-dienone cation **1b,** which if trapped by attack of trifluoroacetate ion at C-2 would (after trifluoroacetylation of the phenol group) yield the observed bistrifluoroacetate **2.** Alternately, trapping of the intermediate 2,5-dienone cation **1a** with a subsequent 1,3 trifluoroacetyl migration to C-2 is also a potential pathway. This consideration, plus the knowledge that an intermediate monotrifluoroacetate was not isolated previously, encouraged us to examine the reaction of 1 with two less active acylating agents, namely acetyl chloride and acetic anhydride.

Results and Discussion

Although prolonged mixing of 4-methylsulfinyl-3,5-xylenol (1) in benzene at room temperature with an excess of acetic anhydride did not initiate any reaction, similar treatment with acetyl chloride eventually brought about complete conversion to two new compounds. The minor compound (18%) was tentatively identified as the 2-chloro analogue **3** on the basis of its spectral data; i.e., NMR studies showed the loss of an aromatic proton, and the mass spectrum indicated incorporation of a chloride atom and a parent ion of *m/e* 202. The major compound (57%) was readily identified by comparison with a known sample as 4-chloro-3,5-xylenol (**4**).[5] A preponderance of this latter product strongly supports the existence of a 2,5-dienone precursor **5** with subsequent aromatization by elimination of –SCH_3 as the major pathway. Failure to isolate such an intermediate and determine its conversion products negated any speculation as to a related reaction sequence culminating in production of the 2-chloro compound **3.**

Since acetic anhydride is a less reactive acylating agent than acetyl chloride, refluxing a mixture of 4-methylsulfinyl-3,5-xylenol (1) in benzene with an excess of acetic anhydride was investigated. Periodic TLC examination indicated that some reaction was taking place, and after 48 h approximately 20% of the sulfoxide (1) had reacted. Preparative TLC of the reaction mixture yielded two new products which could be separated and fully characterized. The major product from this reaction was assigned the structure **6** and would arise from trapping of the 2,5-dienone cation **1a.** The identity of **6** followed from its spectroscopic properties, the infrared spectrum of which showed the absence of hydroxyl functions and the presence of strong carbonyl adsorptions at 1745 (acetate) and 1660 cm^{-1} (cross-conjugated dienone). In accordance with its formulation as a dienone structure, the NMR spectrum of **6** showed that absorption of the two previously aromatic protons (H-2 and H-6) was now shifted upfield from δ 6.60 to δ 6.20. Introduction of an acetate group was also confirmed by NMR spectroscopy. Identification of the minor reaction product as the 2-acetoxy compound **7** (spectroscopic data indicated the presence of a hydroxyl function and just one aromatic proton) suggested a sequential relationship proceeding via a 1,3 acetyl migration in the dienone **6.** Demonstration of this supposition was readily achieved by refluxing a sample of **6** in benzene. This treatment yielded a compound identical in all respects with the previously isolated 2-acetoxy analogue **7.** It was later discovered that in contrast to its sluggish reaction in acetic anhydride–benzene the sulfoxide readily rearranged in a 2:1 mixture of acetic anhydride–acetic acid at 100 °C, but the major product was the 2-acetoxy compound **7.**

The evidence obtained, specifically the transformations effected by acetic anhydride, leads us to conclude that a 2,5-dienone intermediate pathway followed by a 1,3 trifluoroacyl migration most probably accounts for the previously observed reaction of 4-methylsulfinyl-3,5-xylenol (1) with trifluoroacetic anhydride.

Experimental Section

Melting points are uncorrected and were determined on a Kofler hot stage microscope. NMR spectra were recorded on a Varian T-60 NMR spectrometer with Me_4Si as an internal standard. IR spectra were determined as Nujol mulls using a Beckman IR-20A spectrophotometer. Mass spectra were determined on a Perkin-Elmer Hitachi mass spectrometer. Thin-layer chromatograms were run on glass plates coated with silica gel GF. Separated components were detected by UV fluorescence and iodine vapor.

Preparation of 4-Methylsulfinyl-3,5-xylenol. 4-Methylsulfinyl-3,5-xylenol (1) was prepared by oxidation of 4-methylthio-3,5-xylenol with hydrogen peroxide in aqueous acetone at room temperature overnight. The product was purified by recrystallization from ethyl acetate and its identity confirmed by comparison with an authentic specimen.[6]

Reaction of 4-Methylsulfinyl-3,5-xylenol with Acetyl Chloride. A suspension of 4-methylsulfinyl-3,5-xylenol (1; 430 mg) in benzene (10 mL) was treated with an excess of acetyl chloride (0.5 mL) and stirred until thin-layer chromatography studies indicated that the reaction was complete (approximately 1 h). The reaction mixture was then neutralized by decantation into a cold saturated solution of sodium bicarbonate (40 mL). After extraction of the neutral solution with chloroform (2 × 50 mL), the chloroform extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was subsequently purified by preparative thin-layer chromatography (ethyl acetate–hexane, 1:3). Crystallization of the major component (R_f 0.56) from hexane gave 4-chloro-3,5-xylenol (**4;** 183 mg), which had identical NMR, IR, and mass spectra and melting point with an authentic sample.[5] The minor compound (R_f 0.85), 2-chloro-4-methylthio-3,5-xylenol (**3;** 58 mg), was a yellowish oil:

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NMR ($CDCl_3$) δ 6.78 (1 H, s, aromatic H), 2.60 (3 H, s, CCH_3), 2.34 (3 H, s, CCH_3), and 2.17 (3 H, s, SCH_3); MS *m/e* 202 (M^+).

Reaction of 4-Methylsulfinyl-3,5-xylenol with Acetic Anhydride. A suspension of 4-methylsulfinyl-3,5-xylenol (**1**; 410 mg) in benzene (10 mL) was treated with an excess of acetic anhydride (0.5 mL) and refluxed with stirring for 48 h. Workup and purification as outlined for the acetyl chloride reaction afforded one major compound (R_f 0.33) which crystallized from hexane to give the 2,5-dienone **6** (41 mg): mp 110–112 °C; IR (Nujol) 1745, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 6.20 (2 H, s, dienone H), 2.18 (3 H, s, SCH_3), 2.04 (6 H, s, CCH_3), and 1.84 (3 H, s, OAc); MS *m/e* 226 (M^+). Crystallization of the minor compound (R_f 0.76) from hexane gave 2-acetoxy-4-methylthio-3,5-xylenol (**7**; 17 mg): mp 84–85 °C; IR (Nujol) 3310, 1738, and 1565 cm^{-1}; NMR ($CDCl_3$) δ 6.78 (1 H, s, aromatic H), 2.36 (3 H, s, CCH_3), 2.34 (3 H, s, OAc), 2.22 (3 H, s, CCH_3), and 2.16 (3 H, s, SCH_3); MS *m/e* 226 (M^+).

Reaction of 4-methylsulfinyl-3,5-xylenol (**1**) in a 2:1 mixture of acetic anhydride–acetic acid at 100 °C went to completion within an hour. The predominant product was the 2-acetoxy compound **7**, and a trace of the dienone **6** was also isolated.

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Registry No.—**1**, 22454-92-8; **3**, 67030-99-3; **4**, 88-04-0; **6**, 67031-00-9; **7**, 67031-01-0; 4-methylthio-3,5-xylenol, 7379-51-3.

References and Notes

(1) R. Pummerer, *Ber. Dtsch. Chem. Ges.*, **43**, 1401 (1910).
(2) L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, **626**, 19 (1959).
(3) J. Kitchin and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 959 (1972); H. Kosugi, H. Uda, and S. Yamagiua, *ibid.*, 912 (1975); *ibid.*, 71 (1976); L. S. S. Reamour and W. I. O'Sullivan, *ibid.*, 642 (1976); Yuji Oikawa and Osamu Yonemitsu, *J. Chem. Soc., Perkin Trans. 1*, 1476 (1976); G. A. Koppel and L. J. McShane, *J. Am. Chem. Soc.*, **100**, 88 (1978); R. R. King, R. Greenhalgh, and W. D. Marshall, *J. Org. Chem.*, **43**, 1262 (1978).
(4) R. Greenhalgh, W. D. Marshall, and R. R. King, *J. Agric. Food Chem.*, **24**, 266 (1976).
(5) Purchased from Aldrich Chemical Co., Milwaukee, Wis.
(6) Provided by Chemagro, Kansas City, Kans.

Model Studies of Thiamin Catalysis. Inductive Effects of Nitrogen-Bonded Substituents and Influence of Steric Inhibition of Resonance on Kinetic Carbon Acidities of Thiazolium Ions

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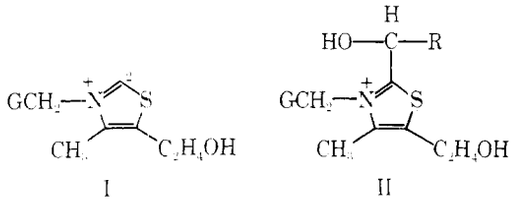
Thiazolium ions are important catalysts both in biological[1] and in chemical systems.[2] Thiamin or vitamin B_1 (I), for example, is involved in a number of transformations involving carbonyl compounds, such as the conversion of acetaldehyde to acetoin.[3] Similarly, other thiazolium salts are useful catalysts in the synthesis of acyloins.[2]



I

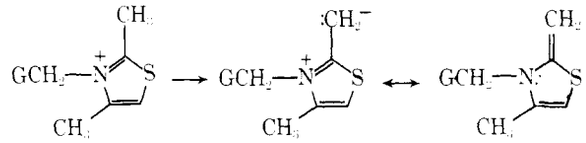
II

I, IIa, G = 4-amino-2-methylpyrimidinyl
IIb, G = H; R = CH_3

Key steps in the mechanism of acyloin formation include deprotonation of a thiazolium ion at position 2 to give an ylide which then adds to a carbonyl electrophile. Resultant intermediate II then is deprotonated at the newly formed side chain to give a second nucleophile, often called an "enamine". Reaction of this enamine with additional carbonyl compound followed by expulsion of ylide gives rise to acyloin product.

On a more detailed level, our current knowledge is very limited. Consideration of the reactivity of a series of substituted thiazolium ions at each step of the multistep sequences reveals that much remains to be learned.

We report results designed to clarify some aspects of this complex mechanism. We have measured the influence of substituents at an annular nitrogen atom on the rates of deprotonation of simple thiazolium ions (III) to produce an enamine (eq. 1). Our results provide an indication of how



III, G = H, C_6H_5, p-$O_2NC_6H_4$, CN (1)

sensitive side-chain deprotonation is to inductive effects of nitrogen-bonded substituents. A second aspects of our study deals with the magnitude of steric inhibition of resonance found when IIb (G = H, R = CH_3) is deprotonated at the 1-hydroxyethyl position.

Results and Discussion

Inductive Effects. Rates of deprotonation of 2,4-dimethylthiazolium ions (III) having groups G = H, C_6H_5, p-$O_2NC_6H_4$, and CN were obtained by studying hydrogen isotope exchange. Loss of a proton from the 2-methyl group to give a resonance stabilized conjugate base, eq 1, was catalyzed by acetate ion buffers in D_2O. Neither water nor deuterioxide compete significantly with acetate ion general base; pseudo-first-order rate constants for deprotonation, k_ψ, can be converted to second-order rate constants k_B reflecting acetate ion catalysis according to the equation

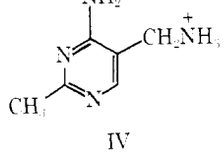
$$k_\psi = k_B[CH_3CO_2^-] \quad (2)$$

Examination of the results in Table I shows that k_B obtained in this way is essentially constant as the concentration of catalyst is varied by as much as tenfold.

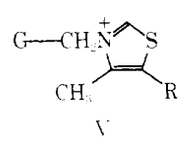
Comparison of the four k_B values reveals that substituents G, in spite of being removed from the thiazolium ring by a saturated carbon atom, have a significant influence on kinetic acidity. Comparing k_B values and using the value for G = H as a reference gives rise to relative rate constants of 1.0, 9.1, 27, and 187 for substituents G = H, C_6H_5, p-$O_2NC_6H_4$, and CN, respectively.

A linear free-energy correlation can be constructed between the logarithm of k_{rel} and pK_a values for substituted methylammonium ions, $GCH_2NH_3^+$,[4,5,8] having the same substituents. The slope of this correlation (correlation coefficient r = 0.962) is −0.40. Electron-withdrawing substituents promote the acidity of both the carbon and nitrogen acids. Naturally, effects are smaller in the case of the carbon acids where proton transfer is less complete. Although electron-withdrawing substituents destabilize both the positively charged carbon acid and the transition state, effects on transition-state energies are smaller because of extensive charge neutralization.

Using the pK_a (8.01) of methylammonium ion IV substituted with a pyrimidine ring as in thiamin and the free-energy



IV



V