The present work in combination with the recently determined photoelectron spectrum of DAD[1b] allows tentative extension of the θ(CSSC)/$\Delta E(n_+-n_-)$ correlation to 111° as depicted in Figure 4. It should be borne in mind that the one-point extrapolation beyond 90° is made with the reservations expressed in the previous section. Direct application of the revised curve to *t*-Bu-SS-*t*-Bu is somewhat tenuous since the literature values for $\Delta E(n_+-n_-)$ range from 0.60[23] to 0.65.[23,25a] Thus we have measured the spectrum once again as the average of several determinations. The result, $\Delta E(n_+-n_-) = 0.63$, implies θ(CSSC) = 121°. Elaboration of the θ(CSSC)/$\Delta E(n_+-n_-)$ relationship to larger values of the S-S dihedral angle awaits the availability of a suitable series of dialkyl disulfides.

Acknowledgment. We are grateful to the Danish Natural Science Research Council for support enabling the purchase of a photoelectron spectrometer.

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Additive Pummerer-Initiated Functionalization of Allylic Methyl Groups in Acrylic Acid Derived Systems

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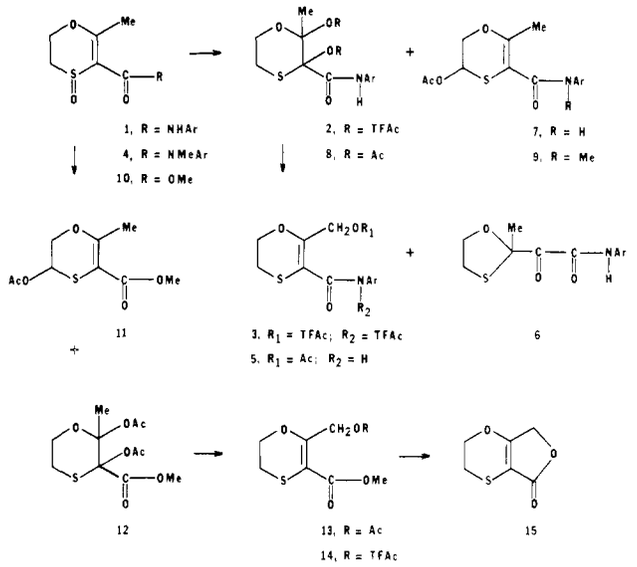
Received July 21, 1980

Elucidation of reaction parameters for the conversion of the additive Pummerer product 2,3-bis(trifluoroacetoxy)-2-methyl-1,4-oxathiane-3-carboxanilide (**2**) to *N*-(trifluoroacetyl)-5,6-dihydro-2-[(trifluoroacetoxy)methyl]-1,4-oxathiin-3-carboxanilide (**3**) was facilitated by substituting an acetic anhydride–acetic acid mixture for trifluoroacetic anhydride in the Pummerer reaction step and by investigating both sets of reaction conditions on 3-(carbomethoxy)-5,6-dihydro-2-methyl-1,4-oxathiin 4-oxide (**10**).

Carboxin (5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide) and structurally related carboxamides are well established as systemic fungicides which can effectively control various smuts and rust diseases.[1] The transformation (for gas–liquid chromatography purposes) of carboxin sulfoxide (**1**; an oxidative metabolite of carboxin) to *N*-(trifluoroacetyl)-5,6-dihydro-2-[(trifluoroacetoxy)methyl]-1,4-oxathiin-3-carboxanilide (**3**) by reaction with trifluoroacetic anhydride (TFAA) (Scheme I) has been reported previously.[2] This novel reaction provided access to previously unavailable 2-(oxymethyl)carboxin analogues for potential structure–activity relationship studies.[3] Mechanistically, it was determined that carboxin sulfoxide (**1**) on treatment with TFAA initially underwent an additive Pummerer reaction[4] to yield the bis(trifluoroacetoxy)-1,4-oxathiane **2**. This compound subsequently rearranged to the allylic trifluoroacetate **3**. Investigations regarding the mode of conversion from compound **2** to **3** suggested a concerted reaction with possible participation of the anilide group.

As a consequence of its potential synthetic utility, attempts to further elucidate reaction parameters for the allylic methyl functionalization step were undertaken. The first approach involved use of a less active acetylating agent (acetic anhydride) in order to enhance the possible isolation of previously undetected intermediates.[5] The second approach involved replacement of the anilide moiety in carboxin sulfoxide with a methyl ester group in order to establish the role, if any, of an active NH group.

Scheme I



Results and Discussion

Carboxin sulfoxide (**1**) in benzene containing a 2:1 mixture of acetic anhydride–acetic acid[5] was refluxed on a steam bath until TLC studies indicated complete reac-

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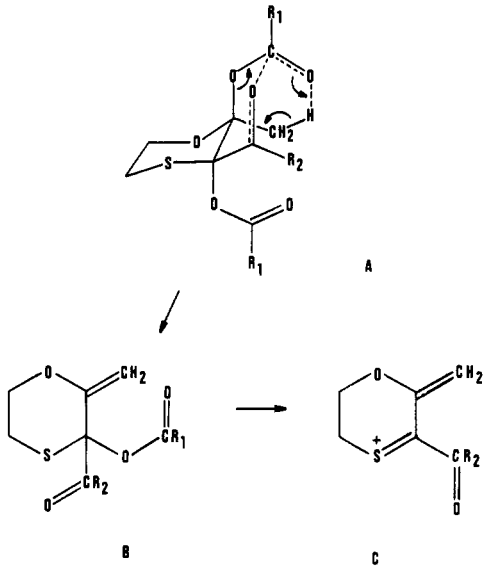
tion of the sulfoxide. Preparative TLC of the reaction mixture yielded four new compounds which were separated, crystallized, and fully characterized. The major product (56% of isolated products) from the reaction was identical as determined by mixture melting point, TLC, and NMR, infrared (IR), and mass spectral data with the 2-acetoxymethyl analogue **5** which had been prepared previously.[2] The least polar compound (14%) similarly proved identical with the previously defined[2] 1,3-oxathiolane **6**. The next least polar compound (16%) was formulated as the 5-acetoxy derivative **7** on the basis of its NMR spectrum.[6] This 5-acetoxy compound is the expected result from a normal Pummerer reaction[7] of carboxin sulfoxide (**1**). An analogous compound was not detected on reaction of **1** with TFAA.[2] NMR and IR data for the most polar product (12%) indicated the presence of two acetate groups in the 2,3-positions (i.e., IR absorption at 1680 cm^{-1} for **1** had shifted to 1705 cm^{-1}). This information supported its formulation as the expected additive Pummerer intermediate **8**. Although the proposed mechanism for the additive Pummerer reaction would predict the possible formation of two diastereoisomers, steric considerations in this instance appear to favor the trans-substitution pattern only. A similar result in a different system has also been reported.[8] Further treatment of **8** with acetic anhydride–acetic acid (in benzene at reflux temperatures) gave a high yield of the allylic acetate **5**. A small quantity of the 1,3-oxathiolane **6** was also produced.

In contrast to the variety of products isolated from treatment of carboxin sulfoxide (**1**) with acetic anhydride–acetic acid, the *N*-methyl analogue **4** under similar reaction conditions gave only one product, and it was characterized as the 5-acetoxy derivative **9**, the expected result from a normal Pummerer reaction.

A related sulfoxide, **10**, without the anilide group, was prepared for comparative investigations by methylation of the carboxin parent acid[9] and hydrogen peroxide induced oxidation of its sulfur moiety. Treatment of **10** with acetic anhydride–acetic acid in a manner analogous to that for carboxin sulfoxide (**1**) yielded (after workup and preparative TLC) three new compounds. The major product (78%) was characterized as the 5-acetoxy derivative **11** and is the expected result from a normal Pummerer reaction. The most polar (on TLC) of the two minor products had spectroscopic properties consistent with the diacetate structure **12**. On further treatment with acetic anhydride–acetic acid it was converted to the second of the two minor compounds, the 2-acetoxymethyl analogue **13** whose structure was readily assigned on the basis of its comparative spectroscopic properties. No 1,3-oxathiolane compounds analogous to **6** were detected in the reaction sequence. Treatment of the sulfoxide **10** with TFAA in benzene at room temperature immediately converted it to one major compound which remained relatively unchanged even at reflux temperatures. Subsequent isolation and spectroscopic evaluation identified it as the 2-(trifluoroacetoxy)methyl derivative **14**. The rapidity of the allylic methyl functionalization step here contrasts sharply with that for the bis(trifluoroacetate) **2** which required benzene

Scheme II



reflux temperatures or overnight at room temperature to effect a similar type of transformation. A possible rationale for the foregoing experimental observations can be summarized as follows.

(a) TFAA enhances the additive Pummerer rearrangement pathway relative to the normal pathway when compared to acetic anhydride. This variation in reaction pathways probably arises from the increased activity of trifluoroacetate anion as a leaving group from the presumed (acyloxy)sulfonium ion intermediate.[10] This would facilitate migration of the 2,3 double bond to the 3,4-position with subsequent acyloxy substitution at C-2, etc.

(b) The degree of activation (or polarization) of the 2,3 double bond would not explain the proportion of additive vs. normal Pummerer products for acetic anhydride which was C(O)NHAr > C(O)OR > $C(O)N(CH_3)Ar$. The observed results would indicate that the NH moiety may have participated (by formation of a hydrogen bond with the incoming reagent or with the sulfoxide group) in the additive Pummerer reaction. This participation was then nullified by replacement of the anilide proton with a methyl group, and no additive Pummerer reaction took place.

(c) In all but one instance the allylic methyl functionalized product was demonstrated to have proceeded directly from an additive Pummerer-rearranged intermediate and not as the result of a "vinylogous Pummerer rearrangement".[11] The preference for initial acyloxy group elimination at C-2 in the sequence was demonstrated by formation of the 1,3-oxathiolane **6**.[2]

Interaction of the C-3 carbonyl moiety (e.g., formulation A in Scheme II) may initiate production of a vinylic intermediate (B) in the reaction pathway.[12] Acid-catalyzed isomerization of B or trapping in a 1,4 manner by acetate ion of a Pummerer-type intermediate C (from elimination of the C-3 acyloxy group) would lead to the observed reaction products.[13]

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The foregoing determinations regarding functionalization of the carboxin 2-methyl group should facilitate other investigations and exploitation of this reaction's potential for the modification of related acrylic acid derived systems.

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 by 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.

Reaction of Carboxin Sulfoxide (1) with Acetic Anhydride–Acetic Acid. A suspension of carboxin sulfoxide (1, 1.5 g) in benzene (50 mL) was treated with an excess of a 2:1 mixture of acetic anhydride–acetic acid (5 mL) and refluxed with stirring until TLC studies indicated that all the sulfoxide had been converted (ca. 80 min). The reaction mixture was then cooled and neutralized by decantation into a cold saturated solution of sodium bicarbonate (200 mL). After extraction of the neutral solution with chloroform (2 × 100 mL), the chloroform extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was subsequently purified by preparative TLC (hexane–ethyl acetate, 2:1). Crystallization of the major component (R_f 0.35) from diethyl ether gave 2-(acetoxymethyl)-5,6-dihydro-1,4-oxathiin-3-carboxanilide (5, 512 mg), which had an identical melting point and NMR, IR, and mass spectra as a sample prepared previously.[2] The least polar compound (R_f 0.74) was similarly identical with 2-methyl-1,3-oxathiolane-2-carbonylcarboxanilide (6, 133 mg). Crystallization of the next least polar compound (R_f 0.49) from hexane yielded 5-acetoxy-5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (7): 145 mg; mp 123–124 °C; IR (Nujol) 3310, 1735, 1655, 1595, 1520 cm^{-1}; NMR ($CDCl_3$) δ 7.38 (5 H, m, Ph) 6.19 (1 H, q, OCHS), 4.35 (2 H, octet, CH_2O), 2.34 (3 H, s, OAc), 2.20 (3 H, s, Me); mass spectrum, m/e 293 (M^+). Crystallization of the most polar compound (R_f 0.26) from diethyl ether gave 2,3-diacetoxy-2-methyl-1,4-oxathiane-3-carboxanilide (8): 116 mg; mp 157–159 °C; IR (Nujol) 3325, 1735, 1675, 1585, 1520 cm^{-1}; NMR ($CDCl_3$) δ 8.12 (1 H, s, NH), 7.34 (5 H, m, Ph), 4.08 (2 H, q, CH_2O), 3.14 (2 H, m, CH_2S), 2.26 (3 H, s, OAc), 2.13 (3 H, s, OAc), 1.91 (3 H, s, Me); mass spectrum, m/e 353 (M^+).

Reaction of 2,3-Diacetoxy-2-methyl-1,4-oxathiane-3-carboxanilide (8) with Acetic Anhydride–Acetic Acid. A suspension of 8 (100 mg) in benzene (10 mL) was treated with an excess of a 2:1 mixture of acetic anhydride–acetic acid (0.5 mL) and refluxed with stirring until TLC studies confirmed that all of the diacetate 8 had been converted (ca. 1 h). Workup and preparative TLC as described for the carboxin sulfoxide (1) reaction yielded the 2-acetoxymethyl derivative 5 (40 mg) and the 1,3-oxathiolane 6 (13 mg). Two minor noncrystalline compounds were tentatively identified by their mass spectra and by mild treatment with base (pyridine) as the *N*-acyl derivatives of compounds 8 and 6, respectively.

***N*-Methyl-5-acetoxy-5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (9).** A suspension of *N*-methylcarboxin sulfoxide (4, 200 mg) in benzene (10 mL) was treated with an excess of a 2:1 mixture of acetic anhydride–acetic acid (1.0 mL) and refluxed with stirring until TLC studies indicated that all of the sulfoxide had been converted (ca. 1.5 h). Workup and preparative TLC as described for carboxin sulfoxide (1) furnished the *N*-methyl-5-acetoxy analogue 9 (161 mg) as an oil: IR (thin film) 1735, 1635, 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (5 H, s, Ph), 5.98 (1 H, q, OCHS), 4.03 (2 H, octet, OCH_2), 3.39 (3 H, s, NMe), 2.08 (3 H, s, OAc), 1.92 (3 H, s, Me); mass spectrum, m/e 307 (M^+).

3-(Carbomethoxy)-5,6-dihydro-2-methyl-1,4-oxathiin 4-Oxide (10). The parent carboxin acid[9] was dissolved in approximately twice its weight of thionyl chloride, and the solution was heated on a steam bath for 15 min. Excess thionyl chloride was removed on a rotary evaporator and 2 molar equiv of anhydrous methanol in benzene was added. After being stirred overnight at room temperature, the mixture was washed with dilute $NaHCO_3$, and the organic layer (after drying over anhydrous Na_2SO_4) was evaporated to dryness. The residue was oxidized with 30% hydrogen peroxide in aqueous acetone (50% molar excess) at room temperature overnight. The product 10 was purified by recrystallization from ethyl acetate: mp 81–82 °C; IR (Nujol) 1705, 1570 cm^{-1}; NMR ($CDCl_3$) δ 4.64 (2 H, 2 d, CH_2O), 3.89 (3 H, s, OMe), 2.90 (2 H, m, CH_2S), 2.49 (3 H, s, Me); mass spectrum, m/e 190 (M^+).

Reaction of 3-(Carbomethoxy)-5,6-dihydro-2-methyl-1,4-oxathiin 4-Oxide (10) with Acetic Anhydride–Acetic Acid. A suspension of 10 (500 mg) in benzene (20 mL) was treated with a 2:1 mixture of acetic anhydride–acetic acid (1.5 mL) and refluxed with stirring until TLC studies indicated that all the sulfoxide had reacted (ca. 50 min). A workup as described for carboxin sulfoxide (1) and preparative TLC (hexane–ethyl acetate, 3:1) isolated the 5-acetoxy analogue 11 (R_f 0.59) as an oil: 261 mg; IR (thin film) 1735, 1710, 1580 cm^{-1}; NMR ($CDCl_3$) δ 6.18 (1 H, q, OCHS), 4.33 (2 H, octet, OCH_2), 3.79 (3 H, s, OMe), 2.40 (3 H, s, OAc), 2.16 (3 H, s, Me); mass spectrum, m/e 232 (M^+). Also isolated from the reaction mixture was the 2,3-diacetate 12 (R_f 0.35) which crystallized (40 mg) from hexane: mp 102–103 °C; IR (Nujol) 1730–1735 cm^{-1}; NMR ($CDCl_3$) δ 4.02 (2 H, q, CH_2O), 3.92 (3 H, s, OMe), 3.15 (2 H, m, CH_2S), 2.20 (3 H, s, OAc), 2.11 (3 H, s, OAc), 1.94 (3 H, s, Me); mass spectrum, m/e 292 (M^+). On further treatment with acetic anhydride-acetic acid 12 converted to the 2-acetoxymethyl derivative 13 (R_f 0.44), a compound that was also present (32 mg) in the original reaction mixture, which was crystallized from hexane: mp 37–38 °C; IR (Nujol) 1730, 1705, 1575 cm^{-1}; NMR ($CDCl_3$) δ 5.13 (2 H, s, CH_2OAc), 4.40 (2 H, q, CH_2O), 3.81 (3 H, s, OMe), 3.00 (2 H, q, CH_2S), 2.10 (3 H, s, OAc); mass spectrum, m/e 232 (M^+).

Reaction of 3-(Carbomethoxy)-5,6-dihydro-2-methyl-1,4-oxathiin 4-Oxide (10) with Trifluoroacetic Anhydride. A suspension of 10 (75 mg) in benzene (5 mL) was treated with TFAA (0.1 mL) with stirring at room temperature. TLC studies indicated that conversion to predominantly one new compound took place immediately. No further change at reflux temperatures was noted. Benzene and unreacted TFAA were removed with a stream of dry N_2, but crystallization of the residue was unsuccessful, and preparative TLC procedures caused large-scale degradation. The crude compound, which had IR (thin film) absorptions at 1790, 1705, and 1575 cm^{-1} and a mass spectral peak at m/e 286 (M^+), was tentatively identified as the 2-trifluoroacetoxy derivative 14. Confirmation of its identity was achieved by dissolution in a 5% pyridine–benzene solution overnight which converted it to the α,β-unsaturated γ-lactone 15.[2]

Acknowledgment. The author thanks G. Lonergan and M. T. Austria, Chemistry Department, University of New Brunswick, Fredericton, New Brunswick, for the NMR determinations and the mass spectral data, respectively.

Registry No. 1, 5234-68-4; 4, 17757-81-2; 5, 42825-80-9; 6, 64754-74-1; 7, 75420-86-9; 8, 75420-87-0; 9, 75458-13-8; 10, 75420-88-1; 10 free acid, 66977-89-7; 11, 75420-89-2; 12, 75420-90-5; 13, 75420-91-6; 14, 75420-92-7; 15, 64754-76-3.

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