Notes

Nucleophilic Vinylic Substitution Approach to Derivatives of Fulvic Acid

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Received December 11, 1985

In the preceding paper, we pointed out the desirability of finding convenient synthetic methods for the preparation of β-chloroalkylidene- and β-chloroarylidenemalonates because they have an activated double bond for potential functionalization by the nucleophilic vinylic substitution (S_NV) approach. In particular, we reported the S_NV reaction initiated synthesis of compounds containing benzopyrone. In our continuing investigation of the synthetic utility of β-chloro malonates, we now report a four-step synthesis of 3-methyl-1*H*,10*H*-pyrano[4,3-*b*][1]benzopyran-1,10-dione by using S_NV reaction between the cyclic β-chloro malonate III and phenol as the key transformation.

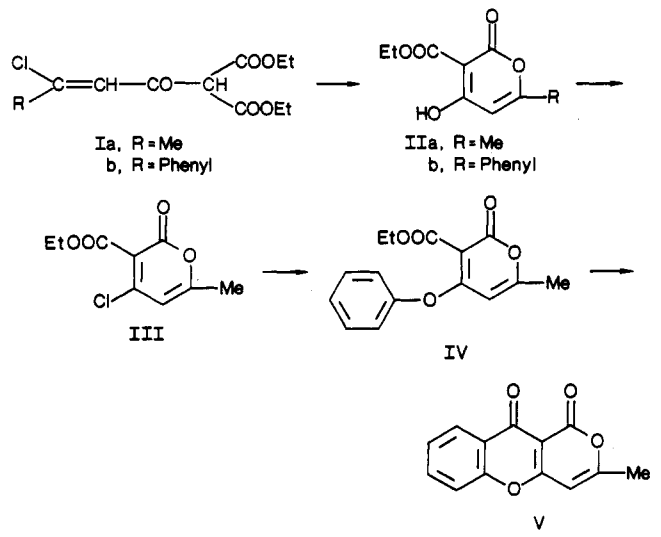
Our interest in the synthesis of 3-methyl-1*H*,10*H*-pyrano[4,3-*b*][1]benzopyran-10-one ring system was stimulated by the fact that 7,8-dihydroxy-3-methyl-10-oxo-1*H*,10*H*-pyrano[4,3-*b*][1]benzopyran-9-carboxylic acid (anhydrofulvic acid) is the key intermediate in the synthesis of the fungal metabolite fulvic acid.[1]

Our method gives a compound that has the critical fused features of fulvic acid. There now remains the substantial task of constructing the correctly substituted precursors so as to complete a more direct synthesis of fulvic acid.

Results and Discussion

A good synthesis of pyrone IIa was required since it was the key intermediate in the synthesis of V. A synthesis of the pyrone has been developed recently,[2] but the method that we used was based on one previously described for the preparation of 2-pyrones from *cis*-5-chloro-2,4-pentadienoic esters.[3] The yield of the heat-catalyzed ring closure was 90%. This cyclization allowed also pyrone IIb to be prepared easily. Chlorination of the 4-hydroxypyrone IIa to 4-chloropyrone III was achieved by heating IIa with phosphorus oxychloride in the presence of tertiary amines.[4] Attempted S_NV reactions between III and phenol by using phenol/potassium carbonate/dimethylformamide or pyridine/Cu_2O (see the preceding paper) were complicated by formation of tarry material, and therefore a milder method was employed with triethylamine/dichloromethane. Ring closure of the ester IV was conveniently effected in concentrated sulfuric acid, a medium that is generally more applicable to corresponding acids (see the preceding paper).

Not surprisingly, the treatment of IV with an excess of polyphosphoric acid also successfully induced the cyclization.



Experimental Section

Melting points are uncorrected, and they were determined on Gallenkampf melting point apparatuses. NMR spectra were recorded with Perkin-Elmer R-12 or JEOL FX-60 spectrometers. $J(H\text{–}CH\text{–}CH_2\text{–}H)$ in the ester groups is 6.8–7.4 Hz and is not explicitly reported. Chemical shifts are reported in parts per million from internal $(CH_3)_4Si$. IR spectra were recorded with Perkin-Elmer 275 IR spectrometers and the wavenumbers are given in reciprocal centimeters. Mass spectra were recorded by M. Reunanen by using direct inlet methods on WG 7070 E instruments. Ethyl 5-chloro-2-(ethoxycarbonyl)-3-oxohex-4-enoate, Ia, and ethyl 5-chloro-2-(ethoxycarbonyl)-3-oxo-5-phenylpent-4-enoate, Ib, were prepared from diethyl mangnesiomalonate and β-chlorocrotonoyl chloride and β-chlorocinnamoyl chloride, respectively.[5] Crude products were used without further purifications.

3-(Ethoxycarbonyl)-4-hydroxy-6-methyl-2-pyrone (IIa). A 100-g sample of crude ethyl-5-chloro-2-(ethoxycarbonyl)-3-oxohex-4-enoate in 0.5 L of xylene is refluxed with stirring until the evolution of ethyl chloride has subsided and is then heated for another hour. The mixture is placed in the refrigerator overnight to give the crude product. Recrystallization from petroleum ether (90–100 °C) gives 68 g (90%) of the product, mp 101–103 °C (lit.[2] mp 101–102 °C). Spectral data is identical with those reported in the literature.[2]

The utilization of the procedure on ethyl 5-chloro-2-(ethoxycarbonyl)-3-oxo-5-phenylpent-4-enoate gives 3-(ethoxycarbonyl)-4-hydroxy-6-phenyl-2-pyrone (IIb), yield 80%. Mp 132–134 °C (from propan-2-ol) (lit.[6] mp 134–135 °C, lit.[7] mp 132 °C). The IR spectrum is identical with that reported in the literature.[7] ^1H NMR ($CDCl_3$): δ 1.35 (t, 3 H), 4.35 (q, 2 H), 6.45 (s, 1 H), 7.15–7.35 (tot, 5 H), 14.0 (1 H). MS, *m/e* calcd for $C_{14}H_{12}O_5$ 260.0681, M^+ 260.0670 (10), 214 (39), 188 (7), 146 (28), 105 (100), 77 (40), 67 (10), 51 (12).

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0022-3263/87/1952-5275$01.50/0

4-Chloro-3-(ethoxycarbonyl)-6-methyl-2-pyrone (III). A 26-g (0.2-mol) sample of diisopropylethylamine is added dropwise with stirring to 40 g (0.2 mol) of 3-(ethoxycarbonyl)-4-hydroxy-6-methyl-2-pyrone in 150 g of phosphorus oxychloride. The mixture is heated at 110 °C with stirring for 5–6 h and is then concentrated as well as possible under vacuum on a rotary evaporator. The residue is extracted three times with 300 mL of ether. The ether is removed on a rotary evaporator. The residue is heated in 250 mL of refluxing petroleum ether (90–100 °C) and decanted while hot. The product (mp 85–86 °C, 32 g) crystallizes. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3 H), 2.22 (s, 3 H), 4.30 (q, 2 H), 6.08 (s, 1 H). IR (KBr): 3080, 2980 (w), 1725 (s), 1625 (m), 1550 (m), 1320, 1240 and 1110 (m). MS, *m/e* calcd for $C_9H_9ClO_4$ 218.0159/216.0189, M^+ 218.0135 (14), 216.0163 (39), 188 (25), 175 (15), 173 (42), 172 (14), 171 (100), 162 (15), 160 (29), 147 (13), 146 (12), 144 (38), 129 (13), 118 (13), 116 (35), 51 (18).

3-(Ethoxycarbonyl)-6-methyl-4-phenoxy-2-pyrone (IV). A 10.3-g (0.11-mol) sample of phenol (p.a. grade) and 15 g (0.12 mol) of dry triethylamine in 50 mL of dichloromethane are added with cooling to 22 g (0.1 mol) of III in 100 mL of dichloromethane, and the mixture is stirred at room temperature overnight (about 12 h). Dichloromethane is removed under vacuum on a rotary evaporator, 200 mL of ether is added, and the flask is shaken vigorously. Triethylammonium chloride is removed by filtration with suction, the ether phase is concentrated under vacuum on a rotary evaporator, about 70 mL of propan-2-ol is added to the residue, and the mixture is placed in a refrigerator. The crude product is collected by filtration. Recrystallization from petroleum ether (90–100 °C) gives 19.2 g, 70% of the product. Mp 104–106 °C. ^{1}H NMR: δ 1.28 (t, 3 H), 2.20 (s, 3 H), 4.28 (q, 2 H), 5.65 (s, 1 H), 6.90–7.55 (tot, 5 H). IR (KBr): 3080 (w), 2990 (w), 1720 (s), 1645 (w), 1565 (m), 1380 (m), 1230 (m), 1070 (m). MS, *m/e* calcd for $C_{15}H_{14}O_5$ 274.0841, M^+ 274.0842 (70), 246 (25), 243 (40), 230 (20), 229 (95), 193 (33), 174 (24), 162 (25), 161 (31), 151 (28), 139 (49), 125 (23), 113 (26), 94 (95), 77 (27), 51 (100).

3-Methyl-1*H*,10*H*-pyrano[4,3-*b*][1]benzopyran-1,10-dione (V). From IV and Concentrated Sulfuric Acid. A 5.0-g sample of IV is heated for 45 min in 30 mL of concentrated sulfuric acid at 100 °C, and then it is poured on ice and filtered. Two recrystallizations from acetic acid give an almost colorless product, yield 3.0 g (72%). Mp 264–266 °C, darkens at 210–230 °C.

From IV and Polyphosphoric Acid. A 1.0-g sample of IV is heated for 30 min in 25 g of polyphosphoric acid and is then poured on ice and filtered. Recrystallization from acetic acid gives 0.52 g (63%) of V. ^{1}H NMR ($CDCl_3$ + TFA): δ 2.50 (s, 3 H), 6.68 (s, 1 H), 7.45–8.48 (tot, 4 H). IR (KBr): 3050 (w), 1720 (s), 1620 (s), 1440 (s), 1170 and 1140 (m). MS, *m/e* calcd for $C_{13}H_8O_4$ 228.0422, M^+ 228.0416 (79), 219 (17), 214 (14), 213 (100), 151 (11), 121 (45), 113 (11).

Acknowledgment. We thank M. Reunanen for mass spectra and P. Pennanen for typewriting.

Registry No. Ia, 110014-13-6; Ib, 110014-14-7; IIa, 58152-49-1; IIb, 92189-06-5; III, 110014-15-8; IV, 110014-16-9; V, 110014-17-0; phenol, 108-95-2.

Electrolytic Transformation of Fluoroorganic Compounds. 2.[1] Generation and Alkylation of a Stable (Trifluoromethyl)malonic Ester Enolate Using an Electrogenerated Base

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Received March 25, 1987

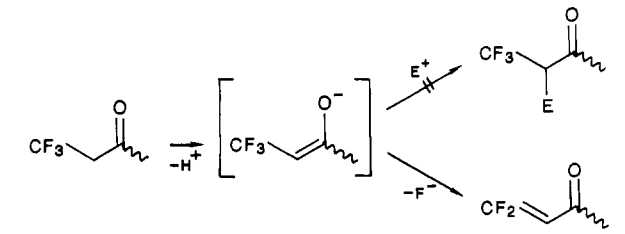
Recently, a number of new synthetic methodologies using trifluoromethyl building blocks have been developed to prepare biologically active compounds bearing a trifluoromethyl group.[2]

Although enolates are versatile building blocks, very few studies reported the use of α-CF_3 enolates because of their instability. These enolates are known to undergo extremely facile defluorination prior to trapping, as indicated in Scheme I.[3-6] The generation of α-CF_3 enolates under conditions where defluorination does not occur remains to be achieved.

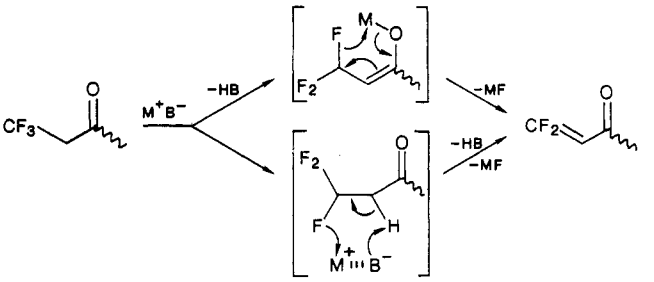
As shown in Scheme II, it is reasonable to assume that the defluorination is assisted by the countercation M^+ of the base used to generate the enolate. Indeed, countercations (M^+) with a strong affinity for the fluorine atom seem to accelerate the defluorination.[3,6] Therefore, it could be anticipated that the use of countercations with a weak affinity for the fluorine atom, such as, for example, quaternary ammonium, phosphonium, and tertiary sulfonium cations, would impede the defluorination reaction.

On the basis of these premises and our continuous interest in organic synthesis using electrogenerated bases (EGBs),[7-10] we have attempted the generation of an α-CF_3

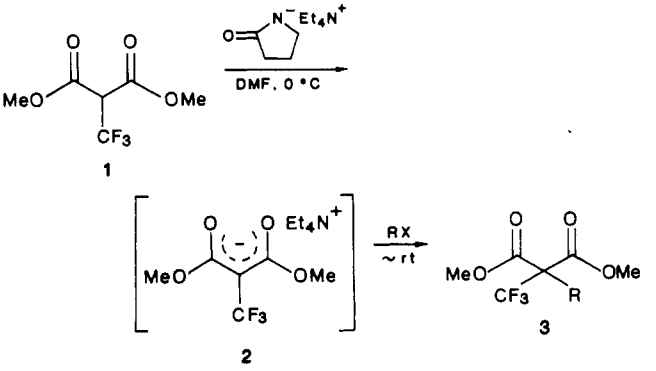
Scheme I



Scheme II



Scheme III



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