A Facile Synthesis of Fulgenic Acid via Base Induced 1,4-Dehydrobromination of (Bromomethyl)methylmaleic Anhydride[1]

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Dedicated to Dr. V. Balasubramaniyan on the occasion of his 66th birthday

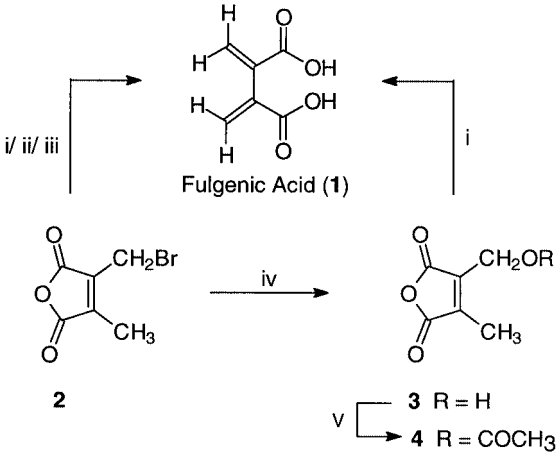
Abstract: A facile synthesis of fulgenic acid (**1**) via 1,4-dehydrobromination of (bromomethyl)methylmaleic anhydride (**2**) using aqueous KOH, *t*-BuOK in THF, and NaH in benzene in 60–85% yield is described. The newly synthesized (hydroxymethyl)methylmaleic anhydride (**3**) also underwent smooth 1,4-elimination in the presence of aqueous KOH to yield **1**.

Key words: (bromomethyl)methylmaleic anhydride, base, 1,4-elimination, fulgenic acid

Butadiene-2,3-dicarboxylic acid (Fulgenic acid, **1**) has been used in studies[2] on the mechanism of action of vitamin B_{12}, in Diels–Alder reactions,[3] and in the preparation of optically pure 2,3-dimethyl succinic acid isomers by asymmetric catalytic reduction,[4] while the corresponding fulgenic anhydride has been recently used in the preparation of tailor-made polymers with material characteristics,[5] such as photochromic light transmissible articles for optical memories and displays. Five alternate synthesis of fulgenic acid (**1**) have been reported in the literature.[3,6–9] The first low-yield synthesis involves[6] a pyrolysis of the dimethyl ester of cyclohexene-1,2-dicarboxylic acid at 700–800°C. A second five-step synthesis with low overall yield based on the pyrolysis of dimethyl α,α-dimethyldiacetyltartrate with two 1,2-elimination reactions at 490°C as a key step has been described.[7] The third four-step synthesis with 10% overall yield[3] employs, pyrolysis of 1,1'-[2,3-bis(ethoxycarbonyl)tetramethylene]dipiperidinium dichloride under 1 Torr pressure at 100°C involving double 1,2-elimination reactions. The fourth one-pot synthesis with 90% yield[8] involves pyrolysis of a diester of cyclobutene-1,2-dicarboxylic acid under high vacuum at 420°C. A fifth five-step synthesis with 37% overall yield has been described[9] starting from triethyl prop-3-ene-1,1,2-tricarboxylate with two oxidative 1,2-eliminations of phenylselenyl moieties using ozone.

Recently, we prepared[10] the (bromomethyl)methylmaleic anhydride (**2**),[11a] by NBS bromination of dimethylmaleic anhydride,[11b] for the synthesis[10] of chaetomellic acid A anhydride. We reasoned that the bromoanhydride **2** would be a potential precursor for the synthesis of fulgenic acid (**1**), via base induced 1,4-elimination[12] of the allylic bromo atom and we herein report a facile approach to **1** (Scheme).

The (bromomethyl)methylmaleic anhydride (**2**) on treatment with aqueous KOH at room temperature, underwent



Reagents and conditions: i) (a) 4 N aq KOH, reflux, 12 h, (b)H^+/H_2SO_4 (60–65%); ii) (a) *t*-BuOK, THF, r.t., 4 h, (b) H^+/H_2SO_4 (80–85%); iii) (a) NaH, benzene, reflux, 4 h, (b) H^+/H_2SO_4 (80–85%); iv) (a) 4 N aq KOH, r.t., 5 h, (b) H^+/H_2SO_4 (86%); v) Ac_2O, H^+/H_2SO_4, r.t., 1 h, (93%)

Scheme

smooth allylic substitution to furnish, the unknown (hydroxymethyl)methylmaleic anhydride (**3**) in 86% yield. The spectral data for **3** revealed that the hydroxy anhydride exists in its free form and does not show any tendency to undergo intramolecular Michael addition to form oxirane or oxetane type of derivatives. The hydroxy anhydride **3** was acylated at room temperature using acetic anhydride in the presence of a catalytic amount of concentrated H_2SO_4 and further characterized as (acetoxymethyl)methylmaleic anhydride (**4**) (93%). The anhydrides **2** and **3** on refluxing with aqueous KOH gave fulgenic acid (**1**) in 60–65% yield via 1,4-elimination. In both the cases the elimination must be taking place on the dipotassium salt of (hydroxymethyl)methylmaleic acid in basic aqueous medium. In another reaction the anhydride **2** on treatment with excess of *t*-BuOK in THF at room temperature gave **1** in 80–85% yield by abstracting the allylic H-atom followed by intramolecular 1,4-elimination of the allylic bromo atom. Similarly, the anhydride **2** on reaction with sodium hydride in refluxing benzene also furnished the fulgenic acid (**1**) in 80–85% yield involving 1,4-elimination of the allylic bromo atom. Amongst all the above mentioned conversions of **2** to **1**, the reaction in benzene using NaH was more clean to handle, as the for-

mation of polymeric impurities was not observed in this reaction. The analytical and spectral data obtained for **1** were in agreement with the reported data.[3,7–9]

In summary, we have demonstrated a base-induced facile synthesis of fulgenic acid (**1**) starting from (bromomethyl)methylmaleic anhydride (**2**) with 60–85% yields, employing an 1,4-elimination of hydrobromic acid.

Melting points are uncorrected. Column chromatographic separations were done on ACME silica gel (60–120 mesh). KOBu-*t* and NaH (60% dispersion in mineral oil) were obtained from Aldrich Chemical Co. Petroleum ether used had bp 60-80 °C.

Butadiene-2,3-dicarboxylic Acid (Fulgenic Acid, 1)

Method A: A solution of (bromomethyl)methylmaleic anhydride (**2**; 1.03 g, 5 mmol) or (hydroxymethyl)methylmaleic anhydride (**3**; 710 mg, 5 mmol) in 4 N aq KOH (12.5 mL) was gently refluxed for 12 h. The mixture was allowed to cool to r.t. and slowly acidified to pH 2, with 6 N H_2SO_4 (10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine and dried (Na_2SO_4). The concentration of organic layer in vacuo at r.t. followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether/EtOAc (6:4) gave pure **1**; yield: 430 to 460 mg (60–65%). [The aqueous layer on further extraction with EtOAc (3 × 10 mL) gave small amount (5–10%) of polymeric white colour residue].

Method B: To a slurry of *t*-BuOK (2.80 g, 25 mmol) in THF (15 mL) was added a solution of the anhydride **2** (1.03 g, 5 mmol) in THF (10 mL) at r.t. with constant stirring under argon atmosphere. The mixture was further stirred for 4 h and diluted with Et_2O (25 mL), brine (10 mL), and then slowly acidified with 6 N H_2SO_4 (5 mL). The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 × 15 mL). The combined organic layer on usual work up and silica gel column chromatographic purification gave pure **1**; yield: 570 to 600 mg (80–85%).

Method C: To a slurry of mineral oil free NaH (600 mg, 25 mmol) in benzene (15 mL) was added a solution of anhydride **2** (1.03 g, 5 mmol) in benzene (10 mL) under argon atmosphere and the mixture was refluxed under stirring for 4 h. The reaction was allowed to reach r.t. and diluted with Et_2O (25 mL), brine (10 mL), and then slowly acidified with 6 N H_2SO_4 (5 mL). The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 × 15 mL). The combined organic layer on usual workup followed by silica gel column chromatographic purification gave pure **1**; yield: 570 to 600 mg (80–85%). Recrystallization from acetone plus chloroform mixture (1:9) gave analytically pure sample of **1**; mp 186–188°C (Lit.[8a] mp 184–187°C); R_f 0.51 (MeOH/EtOAc, 1:1).

IR (nujol): ν = 3145, 1675, 1615 cm^{-1}.

^1H NMR (acetone-d_6, 200 MHz): δ = 5.88 (d, *J* = 1.5 Hz, 2 H), 6.22 (d, *J* = 1.5 Hz, 2 H).

^{13}C NMR (DMSO-d_6, 50 MHz): δ = 126.4, 140.1, 167.0.

MS: *m/z* = 142, 124, 98, 80, 69.

Anal. Calcd for $C_6H_6O_4$ (142.1): C, 50.71; H, 4.26; Found: C, 50.49; H, 4.52.

3-Hydroxymethyl-4-methylfuran-2,5-dione (3)

To an ice-cold solution of 4 N aq KOH (10 mL) was added, (bromomethyl)methylmaleic anhydride (**2**; 2.05 g, 10 mmol) and the mixture was stirred at r.t. for 5 h. The mixture was slowly acidified with 6 N H_2SO_4 (10 mL), and saturated with solid NaCl and stirred at r.t. for 30 min. The aqueous layer was extracted with EtOAc (4 × 20 mL) and the organic layer was washed with brine (20 mL) and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether/EtOAc (3:1) gave pure **3**; yield: 1.22 g (86%); mp 54–56°C.

IR (nujol): ν = 3255, 1800, 1760, cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.22 (s, 3 H), 2.40 (br s ,1 H), 4.63 (d , *J* = 2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 9.9, 55.2, 141.3, 143.4, 165.7, 166.3.

MS: *m/z* = 142, 124, 113, 98, 85, 69, 55.

Anal. Calcd for $C_6H_6O_4$ (142.1): C, 50.71; H, 4.26; Found: C, 50.78; H, 4.33.

3-Acetoxymethyl-4-methylfuran-2,5-dione (4)

A solution of **3** (284 mg, 2 mmol) in Ac_2O (3 mL), was stirred at r.t. in presence of catalytic amount of concd H_2SO_4 for 1 h. The mixture was diluted with Et_2O (30 mL), washed with brine (2 × 10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether/EtOAc (85:15) gave pure **4** (thick oil); yield: 344 mg (93%).

IR (neat): ν = 1860, 1825, 1775, 1685 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.13 (s, 3 H), 2.21 (s, 3 H), 4.97 (s, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 9.5, 20.0, 54.9, 137.0, 144.4, 163.7, 165.1, 169.8.

MS: *m/z* = 184, 142, 124, 113, 98, 67.

Anal. Calcd for $C_8H_8O_5$ (184.2): C, 52.18; H, 4.38; Found: C, 52.39; H, 4.51.

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