Synthesis of 5,7-Dichloro-2*H*-1-benzopyran-2-ol

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The reaction of 4,6-dichloro-2-(methylthiomethoxy)cinnamaldehyde (**3**) or 4,6-dichloro-2-hydroxycinnamaldehyde (**5**) with mercuric chloride in hot aqueous acetonitrile gave 5,7-dichloro-2*H*-1-benzyopyran-2-ol (**4**) in good yield.

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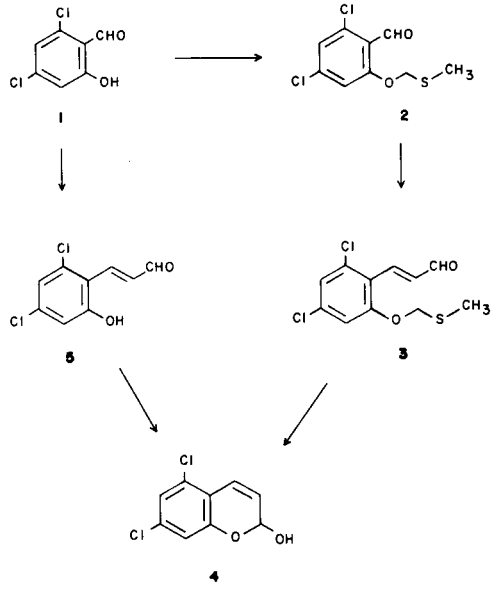
While investigating conditions for unmasking the phenolic moiety of **3**, a new and potentially useful route to 2*H*-1-benzopyran-2-ols was found. Cinnamaldehyde derivative **3** was prepared from salicylaldehyde **1** *via* alkylation with chloromethyl methyl sulfide to yield **2** followed by condensation of the latter with lithio ethylidenecyclohexylamine and subsequent acidic hydrolysis [1]. None of the expected hydroxyaldehyde **5** was obtained when **3** was treated with mercuric chloride in aqueous acetonitrile at 80° for 4 hours [2]. The only product isolated under these conditions was benzopyran **4**. The use of 2,6-lutidine as a buffer or replacement of the mercuric chloride with silver nitrate [3] resulted in no reaction, even after heating the reaction mixtures at reflux for 24 hours.



The possibility that the observed transformation of **3** to **4** could proceed *via* the intermediacy of **5** was examined. Cinnamaldehyde **5** was prepared directly from **1** in the same manner as that used to convert **2** to **3**, however, in this instance, one additional equivalent of lithium diisopropylamide was used. Transformation of **5** into **4** was accomplished readily in quantitative yield in less than 10 minutes with mercuric chloride in aqueous acetonitrile at 80°. Replacement of mercuric chloride by silver nitrate only provided a trace of **4** after 30 minutes, while replacement by dilute aqueous hydrochloric acid or oxalic acid resulted mainly in the retro aldol product **1** with a trace of **4**.

Thus, a new method for the preparation of 2*H*-1-benzopyran-2-ols has been achieved, albeit unintentionally, *via* a mercury-mediated *E* to *Z* isomerization of the antecedent cinnamaldehyde and subsequent ring closure on an adjacent hydroxyl moiety. This method should compliment the only reported route to 2*H*-1-benzopyran-2-ols unsubstituted in the 2 position, which consists of reduction of the corresponding coumarin with lithium hydrido tris(t-butoxy)-aluminate [4].

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The nmr spectra were recorded on either a Varian EM-390 or Varian SC-300 MHz superconducting system spectrometer using tetramethylsilane as the internal reference. Elemental analyses for carbon and hydrogen were determined using a Perkin-Elmer Model 240 elemental analyzer.

2,4-Dichloro-6-(methylthiomethoxy)benzaldehyde (**2**).

Potassium carbonate (15 g, 110 mmoles) was added to a solution of **1** (9.5 g, 50 mmoles) in dimethylformamide (100 ml) at 60°, followed in ½ hour by chloromethyl methyl sulfide (4 ml, 150 mmoles). The mixture was stirred at 55-60° for 4 hours, cooled, and poured into water (1.5 liters). The solid which formed was collected, washed well with water and air dried to give **2** as a yellow powder (8.7 g, 69%), mp 73-75°; An analytical sample was obtained by recrystallization from ethanol-water, mp 75-77°; nmr (deuteriochloroform): δ 2.27 (s, 3H, $-SCH_3$), 5.23 (s, 2H, $-OCH_2S-$), 6.93 (d, H, J = 2 Hz), 7.08 (d, H, J = 2 Hz), 13.57 (s, H, -CHO).

Anal. Calcd. for $C_9H_8Cl_2O_2S$: C, 43.04; H, 3.21. Found: C, 43.12; H, 3.31.

2,4-Dichloro-6-hydroxycinnamaldehyde (**5**).

A. Ethylidenecyclohexylamine.

Acetaldehyde (56 ml, 44.1 g, 1 mole) was added dropwise to cyclohexylamine (121 ml, 99.2 g, 1 mole) at -20° under an atmosphere of nitrogen. During the initial phase of the addition a white solid precipitated but redissolved as the addition was continued. This cold solution was stirred at -20° for 1 hour followed by the addition of anhydrous sodium sulfate (15 g) and removal of the cooling bath. After stirring at ambient temperature for an additional 1 hour the mixture was filtered by gravity and the residue was washed with *ca.* 15 ml of ether. The combined filtrates were dried further over 5 g of anhydrous magnesium sulfate and filtered. The ether was evaporated and the residual oil was distilled to give ethylidenecyclohexylamine as a colorless liquid (79 g, 63%), bp 57-65°/22 mm [1] bp 47-48°/12 mm).

B. 2,4-dichloro-6-hydroxycinnamaldehyde.

A solution of ethylidenecyclohexylamine (2.63 g, 21 mmoles) in dry tet-

rahydrofuran (20 ml) was added dropwise and with stirring to a cold (0°) solution of lithium diisopropylamide (prepared from diisopropylamine 6.05 ml, 42 mmoles and 42 mmoles of *n*-butyllithium), and the resulting solution was stirred for 10 minutes. This solution was then cooled to -78° and a solution of **1** (3.8 g, 20 mmoles) in dry tetrahydrofuran (20 ml) was added dropwise. The red solution was stirred for an additional 15 minutes at -78°, then the cooling bath was removed and stirring continued at ambient temperature for 2 hours. The reaction mixture was poured into ice water (1 liter) and acidified with acetic acid to *p*H *ca.* 6. The mixture was then extracted into ether (2 × 200 ml). The ether extracts were combined and washed with water (2 × 200 ml) and brine and dried over anhydrous magnesium sulfate. Evaporation gave the crude 3-(2,4-dichlorophenyl)-3-hydroxypropylidenecyclohexylamine as a red oil (7.4 g).

A solution of the hydroxyamine in tetrahydrofuran (50 ml) and water (10 ml) containing oxalic acid (7.5 g) was stirred on a steam bath for ½ hour before diluting with water (300 ml). After cooling to *ca.* 0° the sticky solid that formed was filtered off, washed well with water and sucked dry. Chromatography on silica gel (250 g) with chloroform-methanol (50:1) provided recovered **1** (800 mg) in the first 400 ml of eluant. Continued elution provide **5** (1.3 g, 30%) after an additional 400-740 ml, mp 164-165°. An analytical sample was obtained by recrystallization from toluene, mp 169-170° dec; nmr (deuteriochloroform): δ 6.95-7.2 (m, 3H), 7.8 (d, vinyl H, J = 15 Hz), 9.7 (d, H, -CHO, J = 4 Hz).

Anal. Calcd. for $C_9H_6Cl_2O_2$: C, 49.80; H, 2.79. Found: C, 50.28; H, 2.85.

2,4-Dichloro-6-(methylthiomethoxy)cinnamaldehyde (**3**).

This compound was prepared analogously to **5**, starting with **2** (32.1 g, 124 mmoles) except that only a 10% excess (135 mmoles) of lithium ethylidenecyclohexylamine was employed with no additional lithium diisopropylamide. Workup gave **3** as a sticky yellow solid which crystallized from ethanol-water as tiny yellow needles (19.8 g, 57%), mp 104-106°; nmr (deuteriochloroform): δ 2.27 (s, 3H, $-SCH_3$), 5.30 (s, 2H, $-OCH_2S-$), 6.9-7.3 (m, 3H), 7.8 (d, vinyl H, J = 15 Hz), 9.75 (d, H, -CHO, J = 4 Hz).

Anal. Calcd. for $C_{11}H_{10}Cl_2O_2S$; C, 47.67; H, 3.64. Found: C, 47.87; H, 3.67.

5,7-Dichloro-2*H*-1-benzopyran-2-ol (**4**).

A mixture of **3** (550 mg, 2 mmoles), mercuric chloride (800 mg, 3.2 mmoles), water (4 ml) and acetonitrile (16 ml) was stirred on a steam bath for 4 hours. The dark mixture was cooled and distributed between water (100 ml) and ether (150 ml). The ether layer was washed with water (3 × 100 ml) and dried. Evaporation of the ether provided **4** as a tan powder (420 mg, 97%), mp 138-148° dec. Crystallization from toluene gave an analytical sample as tiny tan needles, mp 120-130° dec; nmr (deuteriochloroform): δ 6.038 (dd, H_2, J = 7 and 3 Hz), 6.093 (dd, H_3, J = 9 and 4 Hz), 6.981 (dd, H_8, J = 2 and 1 Hz), 7.096 (d, H_6, J = 2 Hz), 7.109 (dd, H_4, J = 10 and 1 Hz); tlc: R_f = 0.34 on (Whatman MK6F silica, chloroform).

Anal. Calcd. for $C_9H_6Cl_2O_2$: C, 49.80; H, 2.79. Found: C, 49.79; H, 2.83.

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