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NOTE

A ONE-POT SYNTHESIS OF (±)-(RING $^{13}C_6$)-MANDELIC ACID

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Summary

A one-pot synthesis of (±)-(ring $^{13}C_6$)-mandelic acid is reported. [Ring $^{13}C_6$]-benzaldehyde was cyanosilylated with trimethylsilyl cyanide (TMSCN)/ZnI_2. The resulting cyanosilylated adduct was hydrolyzed with concentrated hydrochloric acid without purification. The workup involves evaporation to dryness and extraction of the (±)-(ring $^{13}C_6$)-mandelic acid with hot benzene. After one crystallization, the synthesis produced an overall yield of 65% of (±)-(ring $^{13}C_6$)-mandelic acid that was about 98% pure by HPLC with UV detection.

Key Words: (±)-[ring $^{13}C_6$]-Mandelic acid, [ring $^{13}C_6$]-Benzaldehyde, Styrene, Trimethylsilyl cyanide (Cyanotrimethyl silane), α-[Trimethyl)silyloxy]-(±)-[ring $^{13}C_6$]-benzylnitrile, Polyester resin.

INTRODUCTION

The current interest in mandelic acid (MA) is due to its being a urinary metabolite found in people exposed to styrene. Styrene is widely used in the production of a variety of resins including acrylonitrile-butadiene-styrene (ABS)

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terpolymers, styrene-acrylonitrile (SAN) copolymers, styrene-butadiene copolymer, styrene-butadiene rubber (SBR), and unsaturated polyester resins.[1] The polyester resin contains approximately 40% monomeric styrene (by weight), as much as 10% of which evaporates into the ambient air.[2] The problems related to human styrene exposure are usually investigated by studying the relationship between environmental levels of styrene and its urinary metabolites, MA and phenylglyoxylic acid (PGA). The U.S. Centers for Disease Control and Prevention (CDC) in collaboration with the Texas Department of Health is studying the rate of anencephaly among babies born in Brownsville, Texas; a private laboratory reported finding PGA in the urine of one of these babies. Because of concern that these cases of anencephaly may have been caused by the exposure of mothers to elevated levels of styrene, CDC is measuring the levels of mandelic acid and phenylglyoxylic acid in the urine of these mothers to determine whether they have been exposed to styrene.

Mandelic acid in urine is routinely extracted into ethylacetate and quantified by gas chromatography after derivatization with N,O-bis(trimethylsilyl)-trifluoroacetamide (BSTFA).[3] Since isotope-dilution mass spectrometric quantification allows researchers to compensate for variables in both sample preparation and instrument response, we chose $^{13}C_6$ mandelic acid as an internal standard for accurate quantification. Mandelic acid is generally prepared by the hydrolysis of amygdalin with sulfuric acid or by the hydrolysis of mandelonitrile with hydrochloric acid.[4] Mandelic acid has also been prepared by the hydrolysis of the adduct of benzaldehyde with dichlorocarbene in the presence of a phase-

transfer catalyst.[5] The mandelonitrile has been prepared by the reaction of benzaldehyde with hydrocyanic acid or by the action of sodium or potassium cyanide on the bisulfite-addition product of benzaldehyde.[4]

In this paper, we present a simple, alternate procedure by which a 65% yield of 98% pure (HPLC/UV) $^{13}C_6$ mandelic acid can be produced from $^{13}C_6$ benzaldehyde in in a one-pot preparation. This procedure involves the cyanosilylation of benzaldehyde with trimethylsilyl cyanide/ZnI_2 followed by acid hydrolysis without the intermediate cyanosilylated adduct being isolated.

EXPERIMENTAL

Materials: [Ring $^{13}C_6$] benzaldehyde was purchased from Cambridge Isotopes (Woburn, Massachusetts). Trimethylsilylcyanide and zinc iodide were obtained from Aldrich Chemical Company (Milwaukee, Wisconsin). All chemicals and benzene (Burdick and Jackson Division, Baxter Healthcare Corporation, Muskegon, Michigan) were used without further purification.

Apparatus: Analytical high-performance liquid chromatography (HPLC) was performed by using a Waters (Milford, Massachsetts) Model 600E Solvent Delivary System equipped with a Dynamax (Rainin Instrument Co., Woburn, Massachusetts) 4.6 mm i.d. x 25 cm L column coupled with a Waters 994 Photo Diode Array Detector (Milford, Massachusetts). Mass spectra were recorded on a VG 70-SE high-resolution mass spectrometer (Manchester, England). Nuclear magnetic resonance (NMR) spectra were recorded on a Varian (Palo Alto, California) model

XL-300 FT NMR spectrometer. Melting points were determined by MEL-TEMP (Laboratory Devices, Cambridge, Massachusetts) and are uncorrected.

Procedure: A mixture of [Ring $^{13}C_6$]-benzaldehyde (0.5g, $4.5x10^{-3}$ moles), trimethylsilyl cyanide (0.68g, $5.0x10^{-3}$ moles), and ZnI_2 (10 mg) was magnetically stirred under N_2 for 24 h. The mixture was treated with concentrated hydrochloric acid (8 mL) and kept at room temperature and stirred for an additional 24 h. The reaction mixture was then heated to boiling with a heating mantle to remove water and HCl. The resulting yellow solid mandelic acid was extracted with boiling benzene (3 x 100 mL), and the benzene extract was then concentrated in vacuo to yield a yellow solid. The product was recrystallized from benzene to give a pale yellow crystalline product (480 mg, 65.5%) with the following characteristics: m.p 115-119 °C; ^{1}H NMR ($CDCl_3$): δ 7.6-7.7 (m, J_{13C-H} = 150 Hz), 7.0-7.2 (m, J_{13C-H} = 150 Hz), 5.2-5.23 (m, $J_{13C-C-H}$ = 4.2 Hz); mass spectrum, m/z (relative intensity): 158.1(M^+, 12.2), 113.1(100), 112.1(9.5), 111.1(16.8), 96.1(9), 85.1(72), 84.1(12.5), 83.1(58.5), 55(24), 54(13); high-resolution electron-impact mass spectrometry (HREIMS) m/z 158.0683; calculated for $^{13}C_6{}^{12}C_2H_8O_3$ 158.0675.

High-performance liquid chromatography: For HPLC analysis, a 8 μm, 4.6 mm x 25cm C_{18} column (Rainin, Woburn, Massachusetts) was used. The mobile phase consisted of ammonium acetate buffer (25 mM, pH 3.1)-acetonitrile (20:1, v/v), and the analysis was performed at a flow rate of 0.5 mL/min with detection at 254 nm.

RESULTS AND DISCUSSION

The method described in this paper, which is outlined in Figure 1, involves the direct cyanosilylation of benzaldehyde by a simple reaction of aldehydes or ketones with 1.2 equivalents of trimethylsilyl cyanide with a trace of ZnI_2.[6,7] The solution was stirred for 24 h under nitrogen, after which concentrated hydrochloric acid was added to effect the hydrolysis. The cyanosilylation reaction was

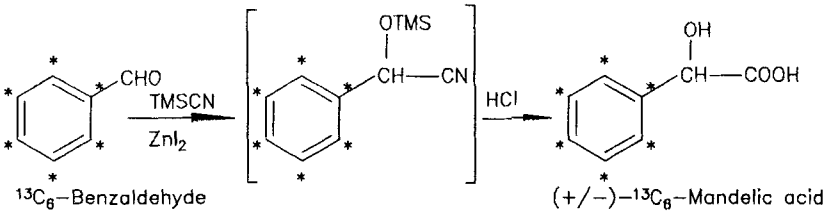

Figure 1

monitored by GC/MS analysis. The mixture was then stirred at room temperature for 24 h. The product was easily extracted with hot benzene and recrystallized from benzene. The reversed-phase HPLC analysis of the final product showed a single peak that had the same retention time (7.98 min) as that of unlabeled authentic mandelic acid. ^{1}H NMR in $CDCl_3$ showed two multiplets in the aromatic region. These two multiplets arose from ^{13}C-H coupling of aromatic protons and resulted in a ^{13}C-H coupling constant of 150 Hz. The benzylic proton that appeared around δ 5.21 also showed long-range coupling due to ring ^{13}C ($J_{13C\text{-}C\text{-}H}$ = 4.2 Hz). HREIMS data [m/z 158.0683 (M^+), Δ 5.2 ppm] showed that the purified product had the molecular formula of $^{13}C_6{}^{12}C_2H_8O_3$.

Mandelic acid has been previously prepared by hydrolysis of mandelonitrile.[4]

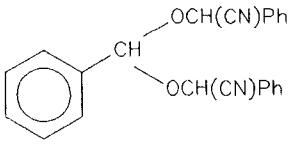

Figure 2

The preparation of mandelonitrile is a two-step process involving the formation of bisulfite adduct of benzaldehyde followed by the reaction of the adduct with potassium or sodium cyanide. When using this method, one should isolate the mandelonitrile and mix it with hydrochloric acid as soon as possible in order to prevent its rapid conversion to the acetal of benzaldehyde and mandelonitrile.[3] (See figure 2.) Cyanosilylation is a convenient abridgement of this method. Although the cyanosilylated adducts are more stable than their cyanohydrin counterparts, the addition of TMSCN to an aldehyde or ketone produces a reaction that is thermodynamically more favorable and higher-yielding than the corresponding HCN-carbonyl addition reactions.[6] The cyanosilylated adduct can be hydrolyzed without any intermediate workup or purification; this process produces a high yield of very pure product.

d_5-Mandelic acid has been prepared by the reaction of d_5-benzaldehyde with dichlorocarbene (chloroform/OH^-) followed by hydrolysis of the intermediate product in the presence of a phase-transfer catalyst.[8] Our method presented in this paper also serves as a convenient general method for preparing α-hydroxy acids because TMSCN readily reacts with various aldehydes and ketones to yield corresponding cyanosilylated adducts.[5] Because of its simplicity, this route may be particularly important in the synthesis of a radioisotope-labeled mandelic acid.

DISCLAIMER

Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

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