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A CONVENIENT SYNTHESIS OF CIS/TRANS-3-CHLOROACRYLIC ACID-UL-^{14}C

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SUMMARY

A convenient method for oxidation of allylic alcohols to the corresponding carboxylic acids is described. A two phase (methylene chloride/aqueous) silver oxide oxidation circumvents isolation of the intermediate aldehydes, thus making the procedure well suited to micro-scale carbon-14 synthesis. Although we required a mixture of cis/trans-3-chloro-acrylic acid-UL-^{14}C and thus began the preparation with cis/trans-3-chloroallyl alcohol-UL-^{14}C, the reaction sequence can be carried out starting with either isomer to provide the isomerically pure carboxylic acids.

Key Words: Carbon-14, 3-chloroallyl alcohol, 3-chloroacrylic acid, oxidation.

INTRODUCTION

Studies on the metabolism/degradation of TELONE* II soil fumigant have provided several polar metabolites. Thus carbon-14 labeled samples of cis/trans-3-chloroacrylic acid were required for spectroscopic and chromatographic comparisons to the metabolites. This communication describes a simple preparation of cis/trans-3-chloroacrylic acid-UL-^{14}C starting with cis/trans-3-chloroallyl alcohol-UL-^{14}C.

DISCUSSION

During the course of studies directed at the stereochemical assignment of β-chlorovinyl carbonyl compounds, Ivanov and coworkers[1] described the conversion of cis/trans-3-chloroallyl alcohol to the corresponding acrylic acids. Jones oxidation (CrO_3, H_2SO_4, ethyl chloride, 5-10°C) of the 3-chloroallyl alcohols gave the 3-chloroacroleins which were distilled in the cold to prevent isomerization and/or resinification (35%). The haloacroliens were then subjected to aqueous silver oxide oxidation providing cis/trans-3-chloroacrylic acid (35%, overall yield 12%). Because of the inherent

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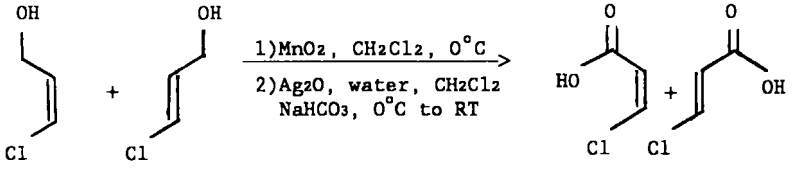
difficulty associated with handling volatile carbon-14 labeled compounds on a microscale, we required a method that would avoid distillation of the aldehyde intermediates. A convenient solution to this problem is as follows: oxidation of a mixture of cis/trans-3- chloroallyl alcohol-UL-^{14}C with manganese dioxide in methylene chloride at 0°C, followed by filtration through Celite provided a clear colorless solution of the aldehyde. Treatment of the 0°C methylene chloride solution with aqueous sodium bicarbonate and silver oxide provided, after filtration and acidification, cis/trans-3-chloroacrylic acid-UL-^{14}C (18%, 98% radiochemical purity).



EXPERIMENTAL

Analysis of the radiolabeled products was achieved by HPLC/UV diode array and radiochemical detection. Instrumentation included the following: Waters model M721 gradient controller, M-45 HPLC pumps, Z-Module and a Novapak C_{18} column; Hewlett Packard 1040A diode array detector and a Packard Trace 7140A radioactivity detector. HPLC analysis of the final products was performed under the following conditions: 0-40 min, 1 mL/min, 100% water; 40-50 min, linear gradient to 100% CH_3CN at 1 mL/min; 50-60 min, 100% CH_3CN, 2 mL/min (each solvent contains 1% HOAc). Direct probe mass spectral analysis of the final product was conducted using a Finnigan 4600 instrument operated at 70 eV ionization potential in the positive ion mode. All reactions were magnetically stirred.

Cis/trans-3-chloroacrylic acid-UL-^{14}C

Cis/trans-3-chloroallyl alcohol (2 mCi, 5.4 mCi/mmol, 0.37 mmol, ca. 55/45 cis/trans) was transferred to a 25 mL round bottom flask using CH_2Cl_2 (4 x 0.5 mL). After chilling to 0°C, MnO_2 (0.7 g total) was added in portions over an 11/h period. The mixture was rapidly filtered through a short column of Celite into a flask cooled in ice. Sodium bicarbonate (40 mg) in water (4 mL) was added and the mixture vigorously stirred at 0°C for 10 min, warmed to room temperature and stirred an additional 2.75 h. The reaction was filtered through a short pad of Celite and the flask and filter washed with saturated sodium bicarbonate (3 x 0.75 mL). The CH_2Cl_2 layer was removed and the aqueous phase extracted with CH_2Cl_2 (2 x 1.5 mL). The aqueous phase was taken to pH 2 with conc. hydrochloric acid and extracted with CH_2Cl_2 (4 x 2 mL). The

CH_2Cl_2 extracts were filtered through layers of $Na_2SO_4/MgSO_4$ and the solvent removed on the rotary evaporator (25 mmHg at ambient temperature) to leave the product as a white solid[2] (7.0 mg, 0.066 mmol, 18%). HPLC retention times: cis-acid, 11.0 min, 67.9%; trans-acid, 24.5 min, 30.6%. Mass spectrum (70 eV, m/e): 110 (0.17%, ^{14}C M^+), 108, 106 (37.0%, 100%, M^+), 91, 89 (36.4%, 90.4%, M^+-OH), 71 (58%, M^+-Cl), 61 (42.0%).

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REFERENCES AND NOTES

1. Ivanov, A.I., Protopopova, T.V., Vanokorov, V.G., and Soldinov, A.P. - Zhurnal Org. Khim., 1; 1748 (1965).

2. The synthetic transformations described were carried out with unlabeled starting materials prior to the labeling synthesis. Each isomer was carried through individually to provide cis-3-chloroacrylic acid, mp 57-59°C [lit. 61-62°C] and trans-3-chloroacrylic acid, mp = 77-79°C [lit. mp 83-84 C).