Preparation and Selective Hydrolysis of Acetal Esters

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ABSTRACT AND SUMMARY

Medium chain length aldehydic acids and esters (C_8-C_{13}) were synthesized by ozonolysis of readily available cyclic and straight chain alkenoate esters followed by rearrangement or reduction of the ozonide. The acetal esters, prepared by reaction of the aldehydic acids with CH_3OH-HCl, were characterized by gas liquid chromatography, proton magnetic resonance, carbon magnetic resonance, thin layer chromatography, and infrared analysis. Selective hydrolysis of the acetal esters to aldehyde esters was conveniently accomplished with H_2O-HCl-CH_3CN to give 95% or higher yields in less than 30 min. Development of this simple and effective hydrolysis procedure allows these medium chain length esters to be safely stored as their acetal esters, which retards their oxidation, trimerization, and decomposition.

INTRODUCTION

The synthesis of isomeric, monounsaturated fatty acids by the Wittig reaction required a series of aldehydic esters for coupling to iodoalkanes (1). The aldehydic esters used for preparation of the 8- and 12-octadecenoic acids were methyl 7-formylheptanoate and methyl 11-formylundecanoate. Common methods available for the esterification of acids include BF_3-etherate (2), methanolic H_2SO_4 (3), methanolic HCl (4), and diazomethane (5). However, for large quantities of aldehydic acids, diazomethane is an impractical method, and acid-catalyzed esterification procedures produce acetal esters instead of aldehydic esters. This paper describes a simple procedure for the preparation of 0.6 to 0.8 moles of the aldehydic esters based on the reaction of aldehydic acids with methanol, concentrated HCl, and trimethyl orthoformate followed by selective hydrolysis of the acetal function. Yields are comparable to, or higher than, previously published methods (6-8) without any hydrolysis of the ester. Preparation of the acetal by this method has previously been described (9), but hydrolysis to the aldehydic ester required the development of solvent systems and reaction conditions which allowed rapid and complete acetal-to-aldehyde conversons without accompanying ester hydrolysis.

EXPERIMENTAL PROCEDURES

Materials

The following known aldehydic acids or esters were prepared by the methods indicated: 7-formylheptanoic and 11-formylundecanoic acids by ozonolysis of the corresponding cyclic olefins, followed by sodium acetate rearrangement of the ozonides (10); methyl 8-formyloctanoate (11), 9-formylnonanoate (12), and 12-formyldodecanoate (12) by ozonolysis and zinc reduction of high oleic safflower methyl esters, methyl 10-undecenoate, and methyl erucate, respectively; methyl 10-formyldecanoate by the Kornblum oxidation of methyl 11-bromoundecanoate (13).

Analytical Methods

Gas liquid chromatography (GLC): An Aerograph Model 550B gas chromatograph equipped with a flame ionization detector was used to follow the acetal to aldehyde interconversion via a 6 ft x 1/8 in., 10% SP-1000, 100/200 mesh, Chromasorb-WAW stainless steel column. The column was operated isothermally at various temperatures between 160 and 195 C with N_2 as the carrier at a flow rate of ∿50 ml/min. These conditions gave chromatograms in 10-15 min. A mixture of the aldehydic esters was analyzed on a 6 ft x 1/8 in. stainless steel column packed with 5% SE-30, 60/80 mesh, Chromasorb W. The conditions used were 110 C with an N_2 flow rate of 50 ml/min.

Thin layer chromatography (TLC): EM Reagents (E. Merck, Darmstadt, Germany) precoated silica gel 60F-254 plates with a layer thickness of 0.25 mm were used. The developing solvent was hexane:Et_2O (60:40, v/v) with visualization by I_2. R_f's indicated an elution order of acetal ester > aldehydic ester >> aldehydic acid.

Infrared analysis (IR): IR spectra were measured in CCl_4 using a Perkin-Elmer 621 Grating infrared spectrophotometer.

Proton magnetic resonance (PMR): PMR spectra were measured in $CDCl_3$ with a Varian HA 100 instrument and a sweep width of 1000 Hz.

Carbon-13 magnetic resonance (C-13): C-13 spectra were measured in $CDCl_3$ with a Brucker WH-90 instrument. An average run consisted of 5000 sweeps with a sweep width of 6000 Hz.

Acetal Formation and Hydrolysis

Methyl 7-formylheptanoate and methyl 11-formylundecanoate: The aldehydic acid (3.0 g; 91% pure) was dissolved in 36 ml methanol (under N_2 blanket) and 5-6 ml of trimethyl orthoformate (TMOF) was added to remove water formed during the reaction. Six drops of concentrated HCl were added while the solution was stirred magnetically at room temperature, and the course of the reaction monitored by GLC (direct injection every 15 min). Aldehydic acids elute as broad tailing peaks from the SE 30 column and are difficult to quantitate. Therefore, in order to determine when the reaction was complete (∿3 hr), an impurity in the sample was utilized as an internal standard to follow the conversion of the aldehydic acid to the acetal ester. The methanol was then removed by rotary evaporator and 20 ml of water, 40 ml of acetonitrile (homogenizing solvent), and 5 drops concentrated HCl were added while the solution was stirred magnetically. After hydrolysis of the acetal was complete (∿15 min by GLC), the sample was extracted with hexane; the extract was washed with water and dried over Na_2SO_4. Stripping and distillation through a 3-in. Vigreux column with Dow Silicon Oil 550 as chaser gave 97% pure aldehydic ester in ca. 90% yield. Larger runs of 0.6 to 0.8 moles increased the yield to 91-92%.

Methyl 8-formyloctanoate, methyl 9-formylnonanoate, methyl 10-formyldecanoate, and methyl 12-formyldodecanoate: The aldehydic ester (3.0 g; 98% pure) was dissolved in 36 ml of methanol and the acetals prepared using TMOF and HCl. Work-up of the acetals for storage, however, required extraction by ether, washing with $NaHCO_3$, and drying over Na_2SO_4. After removal of the ether, the acetal could be stored in this manner (preferred) or distilled. Care had to be taken to remove all of the HCl before distillation or reversion to aldehydic ester, decomposition or condensation would occur. In all of the acetal preparations, 10-15% enol ether by-products were also produced. This presented no problem since both the acetals and the enol ethers were quickly converted to the aldehydic esters upon hydrolysis (∿96% yield). Acetal esters (2.5 g

TABLE I

Physical Properties of Aldehydic Acid Compounds

Compound	Melting point, C		Boiling point, C/mmHg	
	Literature	Found	Literature	Found
$HO_2C(CH_2)_6CHO$	–	42-43	–	129/0.1
$CH_3O_2C(CH_2)_6CH(OCH_3)_2$	–	Liq.[d]	–	80/0.05
$CH_3O_2C(CH_2)_6CHO$	–	Liq.[d]	–	95/0.4
$HO_2C(CH_2)_7CHO$	40-42(14)	–	151/1.5(15)	–
$CH_3O_2C(CH_2)_7CH(OCH_3)_2$	–	Liq.[d]	100-102/1(14)	104/0.07
$CH_3O_2C(CH_2)_7CHO$	–	Liq.[d]	111-112/3(11)	101-102/0.4
$HO_2C(CH_2)_8CHO$[a]	56-57(17)	–	150/0.1(17)	150-151/0.1
$CH_3O_2C(CH_2)_8CH(OCH_3)_2$	–	Liq.[d]	–	137-138/0.25
$CH_3O_2C(CH_2)_8CHO$[b]	–	Liq.[d]	120-121/3 (12)	125/0.8
$HO_2C(CH_2)_9CHO$[c]	–	–	–	–
$CH_3O_2C(CH_2)_9CH(OCH_3)_2$	–	Liq.[d]	–	151/0.6
$CH_3O_2C(CH_2)_9CHO$	–	Liq.[d]	141-143/4(19)	131-133/0.6
$HO_2C(CH_2)_{10}CHO$	64-68(9)	65-66	–	151-153/0.05
$CH_3O_2C(CH_2)_{10}CH(OCH_3)_2$	–	Liq.[d]	–	129-13-/0.05
$CH_3O_2C(CH_2)_{10}CHO$	16(19)	Liq.[d]	154/5(19)	122-123/0.2
$HO_2C(CH_2)_{11}CHO$	87.8(20)	–	–	165/0.05
$CH_3O_2C(CH_2)_{11}CH(OCH_3)_2$	–	Liq.[d]	–	142/0.10
$CH_3O_2C(CH_2)_{11}CHO$	19-20(12)	Liq.[d]	152-153/3(12)	130/0.3

[a] Trimer—mp 113.5 C (16).
[b] Trimer—mo 34-36 (12).
[c] Trimer—mp 126 C (18).
[d] Compound was a liquid at 23 C.

sample) were separated from aldehydic esters, enol ethers, and oxidation products on a 2.5 x 44.5 cm column containing 70 g of silica gel (Baker, 80/200 mesh) upon elution with benzene.

Methyl 11-formylundecanoate from trimer: The acetal was prepared and hydrolyzed in the same manner as methyl 7-formylheptanoate except that excess HCl (∿2x) and heat (30 C) were necessary to solubilize and break up the trimer. Yields of aldehydic ester were ∿90% after distillation.

Analysis of aldehydic acids, acetal esters, and aldehydic esters: PMR and ^{13}C NMR were used primarily for product identification: PMR($CDCl_3$)CPS 230 (t, 2) for $C\underline{H}_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}O$, 330 (s, 6) for $\underset{OC\underline{H}_3}{\overset{OC\underline{H}_3}{CH}}$, 362 (s, 3) for $\overset{O}{\overset{/\!/}{C}}\text{-}OC\underline{H}_3$, 432 (t, 1) $CH_2\text{-}\underset{O}{\overset{O}{C\underline{H}}}$, 974-6 (s, 1) for $\text{-}\underset{O}{\underset{\|}{C}}\text{-}\underline{H}$. ^{13}C NMR ($CDCl_3$) Hertz 768-72 for $\underline{C}H_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}O$, 991 for $\underline{C}H_2\overset{O}{\overset{/\!/}{C}}H$, 1158-63 for $\underset{OCH_3}{\overset{O}{C}}$, 1193 for $\underset{O\underline{C}H_3}{\overset{O\underline{C}H_3}{C}}$, 2369 for $\underset{OCH_3}{\overset{OCH_3}{\underline{C}}}$, 3932-43 for $\underset{O}{\overset{O}{\underline{C}}}$, 4572 -H IR for $\overset{O}{\overset{\|}{\underline{C}}}\text{-}H$. IR ($CCl_4$) cm^{-1} 1065, 1120, 1165, 1190 for $\underset{OCH_3}{\overset{OCH_3}{CH}}$, 1360, 1430 for $\overset{O}{\overset{/\!/}{C}}OCH_3$, 1740 for $\overset{O}{\overset{/\!/}{C}}$, 1710, 3530 for COOH, 3860, 2940 for CHO.

RESULTS AND DISCUSSION

The conversion of aldehydic esters to acetal esters permits storage of these compounds while preventing trimerization and effectively retarding oxidation of the aldehyde. Trimer formation is apparently prevalent in the aldehydic esters and acids and changes in physical properties indicate that it increases with increased chain length. This tendency was noted by a gradual broadening of the melting point and the formation of solids even when stored at -20 C. Since the prepared aldehydic esters were to be used in base catalyzed Wittig syntheses, the formation of stable, base insensitive trimers directly reduced reaction yields. The acetal esters were stored at room temperatures for several months with little change in composition and then quickly hydrolyzed and used. This minimized trimer formation and increased the yields in the Wittig reactions from 40-45% to 55-60%. The rapidity of trimer formation in the longer chain aldehydic esters necessitated immediate use after hydrolysis for best yields.

The melting and boiling points of the aldehydic acid compounds are summarized in Table I. The aldehydic esters through methyl 10-formyldecanoate were found to be liquids at room temperature. Except for methyl 9,9-dimethoxynonanoate, the boiling points of the other acetal esters are new data.

The acetals were easily hydrolyzed provided that a homogenizing solvent was used. The only prerequisite was that the boiling point of the solvent be above that of methanol, thus allowing complete removal of the methanol during the solvent evaporation step and preventing acetal formation during hexane extraction.

The 7-formyl and 8-formyl acetals did not require a homogenizing solvent, but hydrolysis became progressively more difficult for acetals of longer chain length until no reaction occurred for the 11-formyl acetals even after emulsification with aqueous 10% HCl. The use of acetonitrile as a cosolvent significantly increased yields while it decreased the reaction time. Other homogenizing solvents such as tetrahydrofuran, 1,4 dioxane, hexamethylphosphoramide, and methyl ethyl ketone were tested, but only 1,4 dioxane approached acetonitrile in speed and completeness of reaction.

The aldehydic esters produced were analyzed for purity by GLC and IR. NMR, ^{13}C-NMR, and IR were used to determine structural integrity.

The identity of the C_8 to C_{13} aldehydic esters were further established by plotting the log of their GLC retention times against carbon number. Plotting data from separations on a 5% SE 30 column under isothermal conditions yielded a straight line as would be expected for a series of homologous compounds.

The combined procedures involving acetal and ester formation followed by selective hydrolysis are all simple room temperature reactions which give over 90% yields of product. These basic reactions have been demonstrated for the preparation of a series of medium chain aldehydic esters, and further application to other similar compounds should be possible.

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