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The Oxidation of Primary Alcohols to Methyl Esters and Diols to Lactones Using Trichloroisocyanuric Acid

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ABSTRACT

Primary alcohols and diols are easily oxidized to methyl esters by a solution of trichloroisocyanuric acid with methyl alcohol in dichloromethane. In addition, α,ω-diols are also readily oxidized into lactones by refluxing with trichloroisocyanuric acid and pyridine in dichloromethane.

Key Words: Primary alcohols; Methyl esters; Lactones; Diols; Oxidation; Synthesis; Preparation; Trichloroisocyanuric acid.

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Although a variety of oxidizing agents have been shown to successfully convert diols to lactones,[1–8] there are few methods for the synthesis of methyl esters from primary alcohols. *N*-Iodosuccinimide,[7] calcium hypochlorite,[9] and tert-butyl hypochlorite[10] have been shown to oxidize primary alcohols to methyl esters. We wish to report simple procedures for the synthesis of methyl esters from primary alcohols and for lactones from diols using trichloroisocyanuric acid (**1**) [1,3,5-trichloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione] as the oxidizing agent.[11]

Primary alcohols and diols are easily converted into the corresponding methyl esters in a solution of **1** and methyl alcohol in dichloromethane (Eq. (1)). The yield and purity of the isolated methyl esters are shown in Table 1.

$$3ROH + 2C_3N_3O_3Cl_3 + 3CH_3OH \longrightarrow 3RCO_2CH_3 + 2C_3H_3N_3O_3 + 3HCl \quad (1)$$

A reasonable pathway for the transformation is shown in the Sch. 1. Previous studies have shown that the aldehyde to methyl ester conversion[12] is significantly faster than the conversion of primary alcohols to aldehydes.[13]

The primary alcohol to methyl ester conversion is an exothermic reaction, but an increase in reaction temperature results in the formation of byproducts. In addition, there is a variable induction period between the time the reagents are mixed and when the temperature spikes. Characteristically cyanuric acid begins to precipitate as the temperature begins to rise. The oxidation of primary alcohols to methyl esters using **1** was carried out successfully with methyl alcohol in dichloromethane, with methyl alcohol in acetonitrile, and in methyl alcohol. The solvent of choice for moderate or large-scale reactions is dichloromethane because the temperature is controlled internally by the low boiling point. If the temperature is kept at or below 40°C, methanol or acetonitrile can be used as solvents. Since external heat control can be problematic, the recommendation is to use dichloromethane as the solvent and to place the reaction flask in a cold water bath to facilitate heat dissipation. Since chlorine is also present in the reaction mixture, the reaction was protected from light to prevent radical chain chlorination reactions.

A complex mixture of products was formed during the oxidation of phenethyl alcohol and 3-phenyl-1-propanol. Once phenethyl alcohol is oxidized to phenylacetaldehyde, it is expected to have a higher enol content than most aldehydes, and therefore, more likely to form the α-chloro

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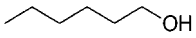
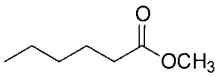
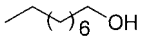
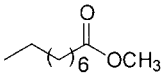
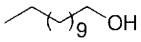
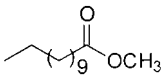
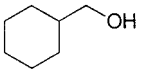
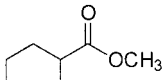
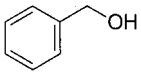
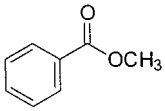
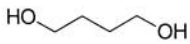
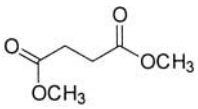
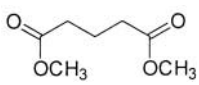
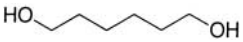
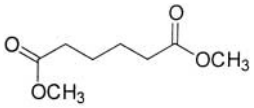
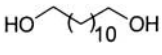
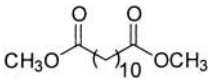
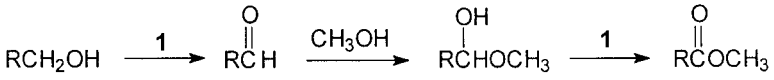
Table 1. The oxidation of alcohols to methyl esters.

Alcohol	Methyl ester	Yield (%)	GC purity (%)
		81[a]	98.9
		81[a]	99.9
		85[a]	99.7
		75[a]	99.9
		79[a]	99.6
		39[b]	87.5
		67[b]	97.6
		96[b]	98.5
		86[b]	99.8

[a]Distilled through a concentric tube column.
[b]Purified by flash chromatography.



Scheme 1.

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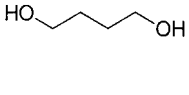
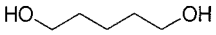
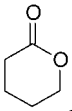
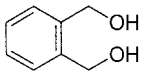
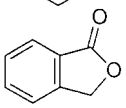
Table 2. The oxidation of alcohols to lactones.

Alcohol	Lactone	Yield[a] (%)	GC purity (%)
		76	98.4
		72	97.4
		97	99.9

[a]Purified by flash chromatography.

derivative. Other byproducts may also result from chlorination on the aromatic ring.[11]

The C_4 and C_5 α,ω-diols can be converted into their corresponding lactones by refluxing with **1** and pyridine in dichloromethane. The yield and purity of the isolated lactones are shown in Table 2. Pyridine is added to absorb the hydrogen chloride formed during the oxidation. Experiments performed without pyridine gave low yields of lactone possibly due to polymer formation. The lactone formation reaction is believed to proceed through a cyclic hemiacetal, which would then be oxidized to the lactone. In contrast, the oxidation of 1,6-hexanediol gave only a trace amount of ε-caprolactone. However, 1,4-butanediol, 1,5-pentanediol, 1,6-hexanediol and 1,12-dodecanediol did oxidize to the corresponding diesters when methyl alcohol was present. The dimethyl succinate from the oxidation of 1,4-butanediol contained an unidentified impurity of 11.3% which may be 2-methoxytetrahydrofuran based on an ^{1}H-NMR peak at 3.23 δ.

EXPERIMENTAL

Analysis by gas chromatography was performed using a Hewlett-Packard 5890 Series II instrument with a 6 ft × 1/8 in 10% Carbowax 20 M column. FT-IR spectra were recorded using a Perkin Elmer 1650. ^{1}H-NMR spectra were recorded on an Anasazi-modified Varian EFT

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90 MHz nuclear magnetic resonance spectrometer in $CDCl_3$ or CCl_4. Flash chromatography was carried out with Merck 60 Å silica gel (230–400 mesh).

All reagents were used as received unless otherwise stated. TCICA was obtained from OMNI with a purity of 99% (88% available chlorine). 1,4-Butanediol and 1,6-butanediol were obtained from J.T. Baker. Phenethyl alcohol was reagent grade from Eastman. All other chemicals were obtained from Aldrich. 1-Nonanol was obtained from Aldrich and distilled prior to use. All products were purified by distillation or flash chromatography and were characterized by comparison with authentic samples using IR and ^{1}H-NMR spectra and GC retention time.

Oxidation of Benzyl Alcohol to Methyl Benzoate

In a 250-mL three-neck flask were placed a magnetic stir bar, 60 mL of anhydrous dichloromethane, 39.0 mL (963 mmol) of anhydrous methyl alcohol, and 22.46 g (96.6 mmol) of **1**. After approximately 10 min of stirring, 10.28 g (10 mL, 95.1 mmol) of benzyl alcohol was added. The flask was flushed with nitrogen, covered with foil to keep out light, and placed in a cold-water bath (~2°C at start of the reaction). After approximately 24 h, excess TCICA was destroyed by the slow addition of saturated aqueous sodium hydrogen sulfite until a negative test with wet potassium iodide-starch test paper was achieved. The cyanuric acid precipitate was removed by vacuum filtration and the solid was washed with pentane. Most of the solvent was removed from the filtrate with a rotary evaporator and the residue was diluted with 60 mL of pentane. The pentane solution was washed with 1 N NaOH (20 mL), saturated NaCl (20 mL), and dried over anhydrous magnesium sulfate. After filtration and concentration, the crude product was vacuum distilled [b.p. 96.0–97.8°C (26.4–30.3 torr)] through a concentric tube column to give 10.16 g (79%) of methyl benzoate. Analysis by GC showed a purity of 99.6%, and the retention time was identical to that of an authentic sample. The IR and ^{1}H-NMR spectra were identical to that of an authentic sample.

Oxidation of 1,4-Butanediol to γ-Butyrolactone

In a 50-mL three-neck flask were placed a magnetic stir bar, 30.0 mL of anhydrous dichloromethane, 0.4544 g (5.042 mmol) of 1,4-butanediol,

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0.90 mL (11.2 mmol) of pyridine, and 1.2899 g (5.550 mmol) of **1**. The flask was flushed with nitrogen, covered with foil to keep out light, and refluxed using a temperature-controlled oil bath. After approximately 5 h, excess TCICA was destroyed by the slow addition of saturated aqueous sodium hydrogen sulfite until a negative test with wet potassium iodide-starch test paper was achieved. The cyanuric acid precipitate was removed by vacuum filtration and the solid was washed with dichloromethane. The solution was washed with 1 N HCl (15 mL). Dichloromethane (2×15 mL) was used to back-extract the HCl wash. The solution was then dried over anhydrous sodium sulfate. After filtration and concentration, the oily residue was purified by flash chromatography to give 0.3305 g (76%) of γ-butyrolactone. Analysis by GC showed a purity of 98.4%, and the retention time was identical to that of an authentic sample. The IR and ^{1}H-NMR spectra were identical to that of an authentic sample.

ACKNOWLEDGMENT

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