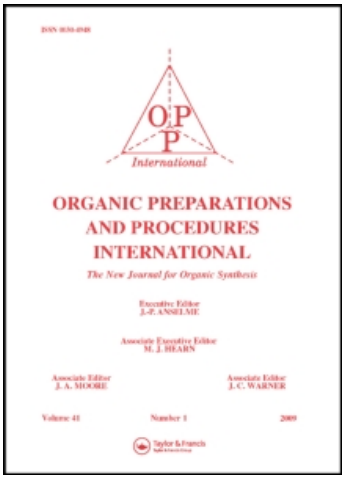

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A NOVEL AND CONVENIENT SYNTHESIS OF 4-HALOBUTYRALDEHYDE ACETALS

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A NOVEL AND CONVENIENT SYNTHESIS OF 4-HALOBUTYRALDEHYDE ACETALS

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(08/02/04)

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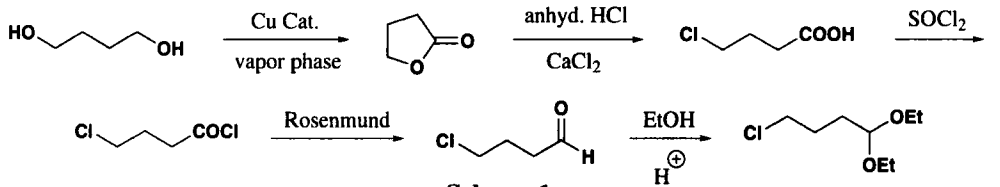
The dimethyl and diethyl acetals of 4-chlorobutyraldehyde and 4-bromobutyraldehyde (1,1-dimethoxy- and 1,1-diethoxy-4-chlorobutane and 1,1-dimethoxy- and 1,1-diethoxy-4-bromobutane) are valuable synthetic intermediates. In particular, these acetals are useful in the Fischer indole synthesis of substituted tryptophols and tryptamines and in the synthesis of natural products.[1] Despite their utility and structural simplicity, there appears to be only one commercial source which makes available small quantities of one of the acetals.[2] The published chemistry for the preparation of these compounds, illustrated for chlorobutyraldehyde diethyl acetal, is rather lengthy and involves a poorly reproducible Rosenmund reduction.[3] Furthermore, in our hands the

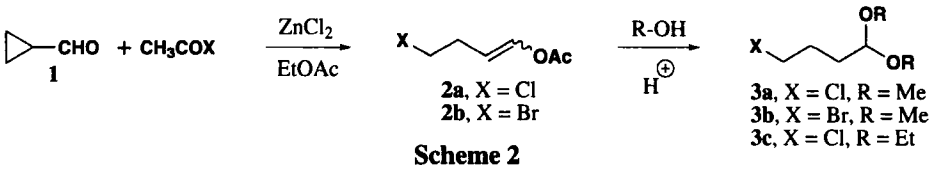


Scheme 1

intermediate 4-chlorobutyraldehyde showed a strong tendency to form a tenaciously stable cyclic trimer upon storage. The overall yield of chloroacetal from this process is typically about 22%.

Other published routes are shorter but involve low-temperature[4] or heavy-metal steps[5] which are problematical to run at large scale. The commercialization of new process technology[6] for air oxidation of butadiene to the corresponding mono-epoxide has made available, in large quantity, cyclopropanecarboxaldehyde (CPCA) (*via* a series of gas-phase conversions).[7] We now report that CPCA can serve as the starting material for a very efficient and convenient new synthesis of 4-halobutyraldehyde acetals.

Reaction of CPCA (**1**) with acetyl chloride in the presence of a catalytic amount of zinc chloride provided an *E/Z* mixture of 4-chloro-1-acetoxy-1-butenes (**2a**) in 75% yield. This cyclopropane ring-opening reaction is reminiscent of the titanium-catalyzed process reported for cyclopropyl ketones by Oshima and coworkers.[8] Compound **2a** has been previously reported only as a low-yield product from the thermal decomposition of a chromium complex.[9] Although Hirsh and coworkers[10] had reported the use of mercuric acetate to catalyze the conversion of enol esters to acetals, we found that the use of a simple resin gave comparable yields. Treatment of **2a** with excess methanol or ethanol in the presence of Amberlyst-15 acidic ion-exchange resin catalyst provided dimethyl and diethyl acetals **3a** and **3c** in 74% and 65% yield, respectively. The corresponding reaction of **1** with acetyl bromide produced the hitherto unreported bromo enol esters **2b** in 79% yield. The corresponding acetal **3b** was formed in 71% yield.



Scheme 2

This work provides a short, convenient route to the methyl and ethyl acetals of both 4-chloro- and 4-bromobutyraldehyde.[11]

EXPERIMENTAL SECTION

Proton NMR spectra were recorded in $CDCl_3$ solvent with TMS internal standard on a Varian Gemini 300 instrument. Gas chromatography (GC) was carried out on an HP 5890 instrument fitted with a 25 m DB-5 column operated from 40°C to 220°C at 10°C/min. Solvents and reagents were used as received from Aldrich Chemical Co. CPCA (**1**) is an Eastman Chemical Company commercial product.

4-Chloro-1-acetoxy-1-butene (2a).- To a stirred solution of 62.4 g (0.80 mole) of acetyl chloride in 750 mL of ethyl acetate at room temperature under nitrogen atmosphere was added in one portion 2.0 g (0.015 mole, 1.8 mol%) of anhydrous zinc chloride. There was then added 56.0 g (0.80 mole) of cyclopropanecarboxaldehyde at such a rate that the temperature of the reaction mixture remained between 40°C and 50°C without external cooling (1-2 hrs). The mixture was

then stirred at 40-45°C for 5 h and allowed to cool to rt. The reaction mixture was washed with aqueous 5% $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Distillation of the crude product through an 8" Vigreux column gave 89.1 g (75%) of a colorless liquid, bp 75-77°C/10 mm Hg. The product was found to consist of a roughly 50/50 *E/Z* mixture by NMR: analysis. IR: (neat) 1760 cm^{-1} (*lit.*[9] IR: 1759 cm^{-1}); ^1H NMR: (δ) 7.1-7.2 (m, 1 H), 5.45 (sextet, 0.5 H), 4.95 (q, 0.5 H), 3.5-3.6 (m, 2 H), 2.63 (q, 1 H), 2.42 (q, 1 H), 2.16 (s, 1.5 H), 2.12 (s, 1.5 H) (*lit.*[9] ^1H NMR: for *Z* isomer: (δ) 7.13 (d, 1 H), 4.93 (q, 1 H), 3.54 (t, 2 H), 2.63 (q, 2 H), 2.16 (s, 3 H)). ^{13}C NMR: (δ) 168.0 (*E*), 167.7 (*Z*), 137.5 (*E*), 136.0 (*Z*), 110.5 (*E*), 109.2 (*Z*), 44.1 (*E*), 43.6 (*Z*), 30.8 (*E*), 28.0 (*Z*), 20.7 (*Z*), 20.6 (*E*) (*lit.*[9] ^{13}C NMR: for *Z* isomer (δ) 167.1, 135.9, 109.2, 43.5, 27.9, 20.7).

4-Bromo-1-acetoxy-1-butene (2b).- A reaction performed as above using 56.3 g (0.46 mole) of acetyl bromide, 2.0 g (0.015 mole) of zinc chloride, and 32.2 g (0.46 mole) of **1** in 350 mL of ethyl acetate provided 70.6 g (80%) of **2b** as a colorless liquid, bp 70-73°C/6 mm Hg. NMR: δ 7.1-7.25 (m, 1 H), 5.42 (m, sextet, 0.5 H), 4.92 (q, 0.5 H), 3.38 (m, 2 H), 2.75 (q, 1 H), 2.56 (q, 1 H), 2.19 (s, 1.5 H), 2.13 (s, 1.5 H).

Anal. Calcd for $C_6H_9BrO_2$: C, 37.33; H, 4.70. Found, C, 37.47, H 4.66

4-Chlorobutyraldehyde Dimethyl Acetal (3a).- A solution of 72 g (0.49 mole) of **2a** in 300 mL of anhydrous methanol (240 g, 7.5 moles) was treated with 15 g of Amberlyst-15 acidic ion-exchange resin and stirred under reflux overnight, at which time GC analysis indicated complete conversion of **2a** to a single major product accompanied by several minor impurities. The catalyst was filtered off and the reaction mixture was treated with 2 g of solid sodium bicarbonate. The volume of the mixture then was reduced to about 75 mL on the rotary evaporator, and the residual bicarbonate was filtered off. Distillation of the filtrate through a 6" Vigreux column gave 55.0g (74%) of a colorless liquid, bp 85-90°C/25mm Hg, *lit.*[3] bp 76-78°C/20 mm. ^1H NMR: (δ) 4.40 (t, 1 H), 3.58 (t, 2 H), 3.32 (s, 6 H), 1.65-1.9 (m, 4 H). (*Lit.*[3] ^1H NMR: (δ) 4.38 (t, 1 H), 3.60 (t, 2 H), 3.30 (s, 6 H), 1.67-1.9 (m, 4 H)).

4-Chlorobutryaldehyde Diethyl Acetal (3c).- Reaction of 13.7 g (0.092 mole) of **2a** with 100 mL of 95% ethanol, 5 g of triethyl orthoformate (added as water scavenger) and 1.40 g of Amberlyst-15 provided 10.8 g (65%) of **4a** as a colorless liquid, bp 45-50°C/1mm Hg. ^1H NMR: (δ) 4.51 (t, 1 H), 3.4-3.8 (m, 6 H), 1.7-1.9 (m, 4 H), 1.10 (t, 6 H). ^1H NMR: of a commercial sample:[2] 4.51 (t, 1 H), 3.4-3.8 (m, 6 H), 1.7-1.9 (m, 4 H), 1.10 (t, 6 H).

4-Bromobutyraldehyde Dimethyl Acetal (3b).- This compound was prepared from **2b** in a manner exactly analogous to the preparation of **3a**. There was obtained a 71% yield of **3b**, bp 64-66°C/6 mm Hg. ^1H NMR: (δ) 4.42 (t, 1 H), 3.46 (t, 2 H), 3.38 (s, 6 H), 1.98 (m, 2 H), 1.80 (m, 2 H) (*lit.*[12] ^1H NMR (CCl_4) (δ) 4.25 (t, 1 H), 3.50 (t, 2 H), 3.20 (s, 6 H), 1.55-2.75 (m, 4 H)).

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