additional 30 min the 0.07 M homogeneous solution was transferred via cannula to the IR cell under argon at −30 °C before recording the IR spectrum.

Acknowledgment. We acknowledge the Natural Sciences and Engineering Research Council of Canada for support of this work through an operating grant to A.C.O. and a postgraduate fellowship to R.D.S.

Registry No. $Me_2Cu(CN)Li_2$, 80473-70-7.

A Facile Procedure for Producing γ-Halo Butyraldehyde Acetals

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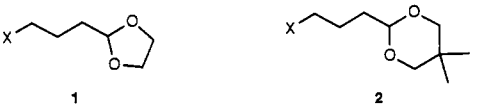
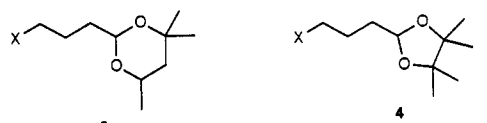
Received October 20, 1991

Four-carbon homologating agents are important in many syntheses. The acetals of 4-halobutanals have been used as alkylating agents to extend molecules by four carbons, while providing an aldehyde function at the new terminus. They have also been converted to Grignard and organolithium reagents and used to prepare 1,5-difunctionality. 1,1-Diethoxy-4-halobutanes[1] and 2-(3-halopropyl)-1,3-dioxolanes, **1a**,[2,3] **1b**,[4] and **1c**,[5] have seen frequent use. 2-(3-Chloropropyl)-5,5-dimethyl-1,3-dioxane, **2a**,[6] has also been used.

Early syntheses of 4-halobutanals began with tetrahydrofurfural and included such intermediates as 5-chloro-1,2-pentanediol, 1,2,5-pentanetriol, and 1,2-epoxy-5-chloropentane.[7,8] In 1961, Pleshakov and co-workers prepared **1a** in 64% yield by hydrogenolysis of 4-chlorobutanoyl chloride, followed by treatment with ethylene glycol in acid.[5e] They also prepared **1c** from **1a** with sodium iodide in acetone in 62% yield. Vedejs and coworkers prepared 4-bromobutanal in 24% overall yield by cleavage of tetrahydrofuran to 4-bromo-1-butanol with HBr, followed by pyridinium chlorochromate oxidation.[9] Kreif and Denis prepared 4-iodobutanal in 46% yield by treating cyclopropanecarboxaldehyde with P_2I_4.[10] Tius and Trehan reduced 4-chlorobutanonitrile with diisobutylaluminum hydride to the aldehyde in 50% yield.[11] Recently, the Pleshakov and Vedejs routes have been used most often, but all of these methods require expensive or less readily available reagents and involve demanding procedures.



1 2



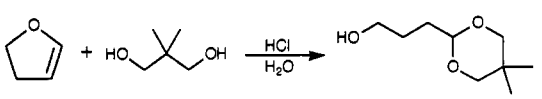
3 4

a, X = Cl
b, X = Br
c, X = I
d, X = OH

The readily available 2,3-dihydrofuran, **5**, is the cyclic enol ether of 4-hydroxybutanal. We proposed that treatment of **5** with an alcohol or diol under appropriate acid conditions might provide acetals of that aldehyde via rearrangement of a 2-alkoxytetrahydrofuran. Solutions of **5** in dry ethanol with a small amount of sulfuric acid gave 2-ethoxytetrahydrofuran or black polymer, but no hydroxy acetal. We then treated **5** with 1,3-propanediol and acid, hoping that the (hydroxypropyl)dioxane would be favored over the alkoxytetrahydrofuran, but only black polymeric material was obtained.

5

Dihydropyran is known to be hydrolyzable in aqueous HCl to the corresponding 5-hydroxypentanal,[12] so we decided to try concurrent hydrolysis of **5** and acetal formation in a substantial amount of water using HCl as catalyst. Although water may seem an unlikely medium for making acetals, we found that **5** and 1,3-propanediol gave about equal amounts of the desired acetal and 2-(3-hydroxypropyl)tetrahydrofuran. It is well-known that methyl groups favor ring formation under equilibrium circumstances;[13] therefore, we treated **5** with 2,2-dimethyl-1,3-propanediol (10% excess) in water with catalytic HCl. We were pleased to find only 2-(3-hydroxypropyl)-5,5-dimethyl-1,3-dioxane, **2d**, in 83% distilled yield (eq 1). In



(eq 1)

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the same way, 2-methyl-2,4-pentanediol gave the corresponding acetal, **3d**, in 76% yield. Pinacol also gave acetal, **4d**, in 82% yield, but in this case, the diol must be added after the hydrolysis of **5**. None of these hydroxy acetals were previously reported in the literature.

We varied the amount of water in an effort to optimize the yield of acetal and found that using less water resulted in a lower yield. When one-third to half the amount of water was used, the yield of acetal dropped sharply to 40–50%. More water had no effect.

The hydroxypropyl acetals were readily converted to the chlorides with thionyl chloride and triethylamine, or to the bromides with phosphorus tribromide. The iodide, **4c**, was prepared from the bromide with sodium iodide in refluxing 2-butanone. The usual Finkelstein conditions using refluxing acetone resulted in only a partial conversion to **4c**.

Homologated products made with these reagents should be readily convertible to the free aldehydes by hydrolysis,[14] trans-acetalization,[15] or used directly in the synthesis of heterocycles,[16] as has been done for other aldehydes protected as di- and trimethyldioxanes.

Experimental Section

Organic reagents were purchased from Aldrich. All ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300.075 and 75.46 MHz, respectively.

2-(3-Hydroxypropyl)-5,5-dimethyl-1,3-dioxane (2d). 2,3-Dihydrofuran (9.27 g, 0.132 mol) was added all at once to a solution of concentrated HCl (3 mL), water (30 mL), and 2,2-dimethyl-1,3-propanediol (15.2 g, 0.145 mol) and then stirred for 10 h. At the end of that time, a drop of phenolphthalein solution was added to the reaction mixture, which was then titrated with 4 M NaOH to the pink end point. The organic layer was separated, and the aqueous portion was extracted with $CHCl_3$ (4 × 20 mL). The extracts were combined, dried with $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Distillation afforded **2d** in 83% yield (19.1 g): bp 85–90 °C (1 mmHg); ^{1}H NMR δ 0.73 (3 H, s), 1.19 (3 H, s), 1.73 (4 H, m), 2.50 (1 H, bs), 3.45 (2 H, d, J = 10.6 Hz), 3.63 (2 H, d, J = 10.6 Hz), 3.65 (2 H, t, J = 5.8 Hz), 4.49 (1 H, t, J = 4.4 Hz); ^{13}C NMR δ 21.82, 22.99, 26.96, 30.11, 31.69, 62.78, 77.25, 101.93.

2-(3-Hydroxypropyl)-4,4,6-trimethyl-1,3-dioxane (3d) was obtained in 76% yield (18.8 g) via the procedure given for **2d**. The hydroxy acetal was sufficiently pure without distillation to be converted to the corresponding halo acetal: ^{1}H NMR δ 1.20 (3 H, d), 1.25 (3 H, s), 1.29 (3 H, s), 1.42 (2 H, d, J = 6.6 Hz), 1.72 (4 H, m), 2.90 (1 H, broad s), 3.64 (2 H, t, J = 5.8 Hz), 3.88 (1 H, m), 4.83 (1 H, t, J = 4.1 Hz); ^{13}C NMR δ 21.66, 22.28, 27.16, 31.56, 32.50, 43.38, 62.83, 68.70, 71.90, 95.15.

2-(3-Hydroxypropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (4d). 2,3-Dihydrofuran (9.27 g, 0.132 mol) was added over 15 min to aqueous HCl (3 mL of concentrated HCl in 30 mL of water), and the resulting solution was stirred for 1 h. Pinacol (18.5 g, 0.157 mol) was dissolved in warm water (30 mL), added dropwise to the solution, and stirred overnight. Isolation according to the method for **2d** afforded 22.0 g (82%) of the crude hydroxy acetal that was then converted directly to the bromo compound: ^{1}H NMR δ 1.21 (12 H, s), 1.70 (4 H, m), 2.69 (1 H, broad s), 3.65 (2 H, t, J = 5.8 Hz), 5.08 (1 H, t, J = 4.7 Hz); ^{13}C NMR δ 22.08, 24.24, 27.58, 33.29, 62.71, 82.01, 100.82.

2-(3-Bromopropyl)-4,4,6-trimethyl-1,3-dioxane (3b). Phosphorus tribromide (43.0 g, 0.159 mol) was added dropwise to freshly distilled DMF (300 mL) under a nitrogen atmosphere, with mechanical stirring. A dark, thick mixture resulted. The hydroxy acetal, **3d** (20.0 g, 0.106 mol), was then added dropwise to the slurry. The mixture was stirred for 24 h at 50 °C and then poured slowly into 600 mL of saturated aqueous K_2CO_3 solution, which was then extracted with CH_2Cl_2 (6 × 25 mL). The extracts were combined, dried with $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Distillation afforded 20.6 g (78%) of the bromo acetal: bp 65–67 °C (0.01 mmHg); ^{1}H NMR δ 1.19 (3 H, d, J = 6.3 Hz), 1.23 (3 H, s), 1.27 (3 H, s), 1.40 (2 H, d, J = 7.5 Hz), 1.71 (2 H, m), 1.99 (2 H, m), 3.44 (2 H, t, J = 6.9 Hz), 3.84 (1 H, m), 4.80 (1 H, t, J = 5.1 Hz); ^{13}C NMR δ 21.73, 22.29, 27.67, 31.66, 33.73, 33.91, 43.48, 68.54, 71.51, 94.42. Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C, 48.13; H, 7.66.

2-(3-Bromopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (4b) was prepared according to the procedure for **3b** (using the same molar amounts). Distillation afforded 20.2 g of the bromo acetal (76%): bp 60–65 °C (0.01 mmHg); ^{1}H NMR δ 1.20 (12 H, s), 1.75 (2 H, m), 1.99 (2 H, m), 3.46 (2 H, t, J = 6.8 Hz), 5.06 (1 H, t, J = 5.0 Hz); ^{13}C NMR δ 22.09, 24.24, 27.85, 33.61, 34.76, 81.85, 100.05. Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C, 48.17; H, 7.65.

2-(3-Iodopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (4c). Acetal **4b** (1.0 g, 0.0040 mol) was added to a magnetically stirred solution of sodium iodide (0.90 g, 0.0060 mol) in 100 mL of 2-butanone. The solution was heated at reflux overnight, and then the solvent was removed by rotary evaporation. Water (100 mL) was added to the residue, and the resulting mixture was extracted with hexane (3 × 20 mL). The extracts were combined, dried with $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Distillation afforded 1.1 g (92%) of **4c**: bp 67–68 °C (0.05 mmHg); ^{1}H NMR δ, 1.19 (6 H, s), 1.20 (6 H, s), 1.70 (2 H, m), 1.96 (2 H, m), 3.24 (2 H, t, J = 7.0 Hz), 5.06 (1 H, t, J = 5.0 Hz); ^{13}C NMR δ 6.57, 22.11, 24.26, 28.68, 37.07, 81.81, 99.89. Anal. Calcd for $C_{10}H_{19}IO_2$: C, 40.28; H, 6.42. Found: C, 40.64; H, 6.47.

2-(3-Chloropropyl)-5,5-dimethyl-1,3-dioxane (2a). Acetal **2d** (10.8 g, 0.0620 mol), triethylamine (6.3 g, 0.062 mol), and 100 mL of toluene were added to a flask fitted with a reflux condenser, an addition funnel, and a magnetic stirrer. The temperature of the mixture was then lowered to 0 °C with an ice bath, followed by the dropwise addition of thionyl chloride (7.4 g, 0.062 mol) over 20 min. After the addition, the mixture was heated at reflux for 1 h. It was then cooled and washed successively with water, 10% aqueous HCl, saturated aqueous $NaHCO_3$, and then water. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Distillation afforded 9.3 g (78%) of **2a**: bp 65–70 °C (0.2 mmHg) (lit.[6] bp 78 °C (0.2 mm)); ^{1}H NMR δ 0.72 (3 H, s), 1.18 (3 H, s), 1.78 (2 H, m), 1.93 (2 H, m), 3.42 (2 H, d, J = 10.7 Hz), 3.56 (2 H, d, J = 10.7 Hz), 3.59 (2 H, t, J = 6.5 Hz), 4.47 (1 H, t, J = 4.7 Hz).

Registry No. **2a**, 65984-84-1; **2d**, 59214-95-8; **3b**, 138923-99-6; **3d**, 59214-99-2; **4b**, 138924-00-2; **4c**, 138924-01-3; **4d**, 138924-02-4; **5**, 1191-99-7; 2,2-dimethyl-1,3-propanediol, 126-30-7; pinacol, 76-09-5.

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Chemistry of Novel Compounds with Multifunctional Carbon Structure. 7.[1] Synthetic Studies of the Potentially Versatile Monofluoro Molecules, α-Functionalized α-Fluoro-β-keto Esters

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Received November 21, 1991

Introduction

The chemistry of organofluorine compounds has made rapid progress during the last decade owing to the development of relatively selective methods for fluorination,[2]

(1) For Part 6, see: Takeuchi, Y.; Ogura, H.; Ishii, Y.; Koizumi, T. *Chem. Pharm. Bull.* **1990**, *38*, 2404.

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