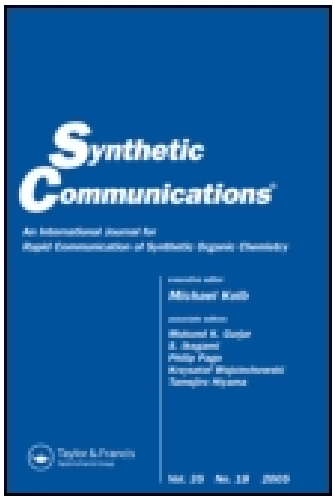

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EFFICIENT PREPARATION OF 2-METHYL-1,3-DIOXOLANE-2-ETHANOL AND 2-(2-BROMOETHYL)-2-METHYL-1,3-DIOXOLANE FROM 4-HYDROXY-2-BUTANONE

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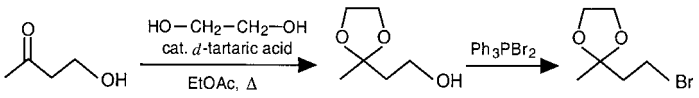
ABSTRACT

2-Methyl-1,3-dioxolane-2-ethanol was prepared in 90% isolated yield from 4-hydroxy-2-butanone and ethylene glycol using a weak acid catalyst and ethyl acetate as the reaction solvent. 2-(2-Bromoethyl)-2-methyl-1,3-dioxolane was prepared in 75% isolated yield by bromination of 2-Methyl-1,3-dioxolane-2-ethanol with dibromotriphenylphosphorane. The reagent was prepared *in situ* by titrating triphenylphosphine with bromine at an ice–ethanol bath temperature.

*Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may also be suitable.

The target compounds are useful methyl vinyl ketone equivalents.

Methyl vinyl ketone equivalents such as 2-methyl-1,3-dioxolane-2-ethanol (**1**)[1] and 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**2**)[2] are vital for use in the formation of rings via a Robinson annulation strategy.[3] Compound **1** has been used in the preparation of the sex pheromone of the western pine beetle, *Dendroctonus brevicomis* Le Conte.[4] Robinson annulation in the presence of an acid has been reported using compound **1**.[5] Compound **2** has also been used in the synthetic pathway leading to the male-produced sex pheromone of the Mexican fruit fly, *Anastrepha ludens* Loew, and the Caribbean fruit fly, *Anastrepha suspensa* Loew;[6] and it has also been used in annulation[3] as well as Grignard[7,8] chemistries. Preparation of compounds **1** and **2**, in high yield and purity, would be beneficial.



Compound **1** has been prepared directly from 4-hydroxy-2-butanone with hydrous zirconium oxide, but the yield was only 28%.[9] A compound [2,5,5-trimethyl-2-(2-bromoethyl)-1,3-dioxane], similar to **2**, has been prepared from a solution of methyl vinyl ketone in benzene using gaseous HBr to afford 4-bromo-2-butanone, which was subsequently converted to the desired bromoketal using a mixture of neopentanediol, triethylorthoformate, and *p*-toluenesulfonic acid.[10] Fractional distillation was required to purify the product and the isolated yield was only 54%.[10] Compound **2** was prepared from methyl vinyl ketone via 4-bromo-2-butanone, using relatively expensive bromotrimethylsilane as the brominating agent.[11] Although the isolated yield was good (82%), the solvent was benzene.[11] Unfortunately, either chromatography on basic alumina gel (Al_2O_3/basic Brockman II) or fractional distillation was required to purify the product.[11]

In this paper, we report the direct conversion of 4-hydroxy-2-butanone to **1** in high yield (improved from 28[9] to 90%), using a weak acid catalyst in ethyl acetate for the ketalization process. The facile conversion of **1** to **2** in good yield with dibromotriphenylphosphorane (Ph_3PBr_2) is also reported. Neither column chromatography nor tedious fractional distillation are required in the workup for the preparation of either **1** or **2**.

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RESULTS AND DISCUSSION

Direct preparation of compound **1** from 4-hydroxy-2-butanone usually results in low yield because of acid-catalyzed dehydration to give methyl vinyl ketone.[9] It was reasoned that the yield of compound **1** could be improved if a weak acid catalyst were used. The formation of 1,3-dioxolanes from aldehydes has been reported to occur in high yield using tartaric acid ($pK_a = 2.93$) as catalyst.[12] Acetalization of aldehydes was conducted in refluxing benzene with anhydrous $MgSO_4$ present to remove the water forming during the reaction and thus improve the isolated product yield.[12]

Less-toxic ethyl acetate could replace benzene as the solvent for ketal formation. Acetylation of either 4-hydroxy-2-butanone or ethylene glycol was not observed. Anhydrous $MgSO_4$ was more finely dispersed in refluxing ethyl acetate than in refluxing benzene; therefore, is less likely to cause bumping. Magnetic stirring was used in this reported synthesis, but the use of mechanical stirring would be recommended for larger batches.

It is necessary to separate compound **1** from unreacted ethylene glycol in the workup. The task is not trivial since both substances have high water as well as ethyl acetate solubility. Ethyl acetate was removed by rotary evaporation and the oily residue was dissolved in CH_2Cl_2. Ethylene glycol is practically insoluble in CH_2Cl_2;[13] so it could be washed away using a small volume of a saturated aqueous $NaHCO_3$ solution. Because of the high water solubility of compound **1**, it was necessary to back-extract the aqueous wash with CH_2Cl_2. Removal of ethylene glycol by this method eliminated the need for tedious fractional distillation.

The preparation of compound **2** from compound **1** required bromination of the alcohol moiety in the presence of the acid-labile ketal function. It was reasoned that this could be accomplished with Ph_3PBr_2 because this reagent has been used to brominate *cis*-homoallylic alcohols containing a ketal function.[14] The hygroscopic reagent Ph_3PBr_2 was very difficult to handle in the open air. When water comes in contact with the reagent, HBr is formed, and direct use of commercially available Ph_3PBr_2 resulted in considerable cleavage of the ketal protecting group. To avoid these problems, Ph_3PBr_2 was prepared *in situ* by titrating triphenylphosphine with bromine in a vessel cooled in an ice–ethanol bath and provided an inert atmosphere. This procedure resulted in a good yield of compound **2** with very little loss of the ketal protecting group.

In summary, compounds **1** and **2** have been prepared in very good yield and high purity without the need for either column chromatography or tedious fractional distillation. The preparative routes to these important synthetic intermediates have been conducted on a multigram scale.

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EXPERIMENTAL

General Details

Ethyl acetate, acetonitrile and pyridine were sufficiently dried by storage over 4 angstrom molecular sieves prior to use. Kugelrohr boiling points are given as the oven temperature at which the product begins to distil. Organic chemicals were purchased from Aldrich (Milwaukee, WI) unless otherwise stated.

Preparation of 2-Methyl-1,3-dioxolane-2-ethanol (1)

Over a period of 10 min, anhydrous ethylene glycol (12.4 g, 200 mmol) was added to a 500 mL round-bottomed flask containing 4-hydroxy-2-butanone (10.2 g, 116 mmol; Lancaster Synthesis, Windham, NH), *d*-tartaric acid (90 mg, 0.6 mmol), and anhydrous $MgSO_4$ (4.0 g, 33 mmol), in dry ethyl acetate (150 mL). The flask was then equipped with a Dean-Starke adapter and condenser, and a nitrogen atmosphere was introduced. A small amount of anhydrous $MgSO_4$ (1 g) was placed into the bottom of the Dean-Starke adapter prior to use, in order to further remove water (reaction byproduct) that azeotropes with ethyl acetate. The mixture was heated to reflux for 16 h then allowed to cool. Solid $NaHCO_3$ (420 mg, 5 mmol) was added to neutralize the acid, and the mixture was stirred for 30 min. The reaction mixture was then filtered and the filter cake was washed with ethyl acetate (10 mL × 3). The solvent was evaporated *in vacuo* and the oily residue was dissolved in CH_2Cl_2 (200 mL). The solution was washed with saturated aqueous $NaHCO_3$ solution (10 mL) to remove unreacted ethylene glycol. The aqueous $NaHCO_3$ solution was back-extracted with CH_2Cl_2 (20 mL × 3) and the CH_2Cl_2 phases were combined. After drying over anhydrous $MgSO_4$ and a small amount of anhydrous $NaHCO_3$, the solvent was evaporated *in vacuo* to give a pale yellow oil (14.1 g). The crude product was distilled (Kugelrohr), to afford a clear, colorless liquid (13.7 g, 90% yield). Purity was checked by gas chromatography (GC) and found to be >98% before distillation and >99% after distillation. b.p. 56°C @ 2.5 mmHg. Lit.,[5] b.p. 135–139°C @ 15 mmHg. MS *m/z* (% base) 131 (M^+-1, 2), 117 (20), 99 (14), 87 (100), 73 (6), 55 (4), 43 (56). ^{1}H NMR δ 1.34 (3H, s, -CH_3), 1.93 (2H, t, $J = 5.5$, -CH_2-CH_2-OH), 3.68 (1H, s, -OH), 3.74 (2H, t, $J = 5.5$, CH_2-CH_2-OH), 3.97 (4H, s, -O-CH_2-CH_2-O-). ^{13}C NMR δ 23.8 (-CH_3), 40.2

(-CH_2-CH_2-OH), 58.9 (-CH_2-CH_2-OH), 64.7 (-O-CH_2-CH_2-O-), 109.0 (-C-$(OR)_2$-).

Preparation of 2-(2-Bromoethyl)-2-methyl-1,3-dioxolane (2)

To a 500 mL round-bottomed flask containing **1** (10.5 g, 80 mmol), triphenylphosphine (27.3 g, 104 mmol) and anhydrous pyridine (9.6 g, 121 mmol) in dry acetonitrile (185 mL) under a nitrogen atmosphere at −10 to 0°C (ice–ethanol bath), bromine (17.1 g, 107 mmol in 15 mL of dry acetonitrile) was added dropwise until a pale yellow color persisted. (The color turns to bright yellow if an excess amount of bromine is added in this titration step). The addition funnel containing any excess bromine is quickly removed and the inert atmosphere is restored. The reaction mixture is allowed to warm to room temperature gradually over the course of 1.5 h under a nitrogen atmosphere. The light yellow color fades during this time as the excess bromine dissipates. The solvent was evaporated *in vacuo* to give a nearly solid mass composed of mainly triphenylphosphine oxide. The nearly solid mass was extracted with hexane (80 mL × 5) by adding the solvent and stirring vigorously for 30 min before collection of the solvent by decantation. In the course of acetonitrile evaporation *in vacuo*, some (approx. 2%) of the product **2** was also distilled over. This was recovered by an evaporation *in vacuo*, of the collected acetonitrile. The recovered product was added to the combined hexane extracts. The extracts were washed with saturated aqueous NaCl solution (10 mL) then with a solution of 0.1 M $CuSO_4$ (10 mL × 3); the aqueous copper solution no longer turned deep blue due to a copper–pyridine complex during the final wash. The combined aqueous copper wash was back-extracted with hexane (20 mL × 2). The hexane solution was dried over a mixture of anhydrous Na_2SO_4 (neutral drying agent added first to remove most of the water) and anhydrous $MgSO_4$ (slightly acidic, but more efficient, drying agent added 15 min later) and stored overnight in the freezer to precipitate most of the remaining triphenylphosphine oxide byproduct of the reaction. After filtration, the solvent was evaporated *in vacuo* to give a pale yellow oil (12.8 g). The crude product was distilled (Kugelrohr), to afford a clear, colorless liquid (11.3 g, 75% yield). Purity was checked by gas chromatography (GC) and found to be >95% before distillation of >99% after distillation. b.p. 52°C @ 2.6 mmHg; lit.,[11] b.p. 42–46°C @ 0.4 mmHg. MS *m/z* (% base) 181 (M^+-15, 17), 179 (M^+-15, 17), 137 (5), 135 (5), 109 (8), 87 (100), 55 (11), 43 (49). ^{1}H NMR δ 1.32 (3H, s, -CH_3), 2.27 (2H, t, $J = 8.3$, -CH_2-CH_2-Br), 3.40 (2H, t, $J = 8.3$, -CH_2-CH_2-Br), 3.94 (4H, m, -O-CH_2-CH_2-O-).

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^{13}C NMR δ 23.9 (-CH_3), 26.7 (-CH_2-CH_2-Br), 42.8 (-CH_2-CH_2-Br), 64.5 (-O-CH_2-CH_2-O-), 110.0 (-C-$(OR)_2$-).

Analysis of Reaction Products

All reactions were monitored by GC using a Hewlett-Packard (HP) 5890 Series II instrument equipped with flame ionization detector and interfaced to a HP ChemStation data system. The oven temperature was programmed from 50 to 250°C at 10°C/min; the programmable cool on-column inlet temperature was always 3°C hotter than the oven temperature and the detector temperature was 250°C. A DB-1 capillary column (15 m × 0.25 mm, 0.25-μm film thickness, J&W Scientific, Folsom, CA) was used with 1 μL sample injections.

Electron impact mass spectra (70 eV) were obtained with an HP 5973 MSD instrument, equipped with a splitless injector. The oven temperature was programmed from 50 to 250°C at 10°C/min; the injection temperature was 250°C and the detector temperature was 250°C. An EC-1 capillary GC column (30 m × 0.25 mm, 0.25-μm film thickness. Alltech, Deerfield, IL) was used with 0.3 μL sample injections. Proton NMR spectra ($CDCl_3$) were obtained on a Bruker (Bellerica, MA) Advance 400 spectrometer at 400 MHz. Chemical shifts are referenced to tetramethylsilane; coupling constants (J) are in hertz.

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