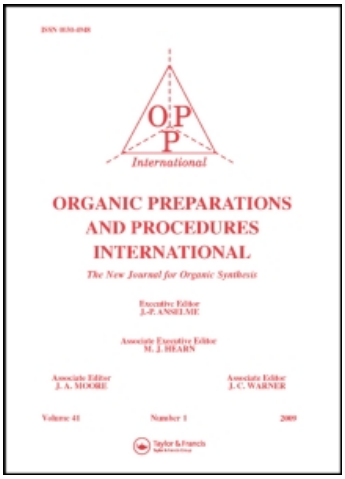


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

1,3-PROPANEDIOLS FROM KETONES BY FORMYLATION AND REDUCTION

D. E. Pearson[a]; John D. Weaver[a]
[a] Department of Chemistry, Vanderbilt University, Nashville, TN

To cite this Article Pearson, D. E. and Weaver, John D.(1978) '1,3-PROPANEDIOLS FROM KETONES BY FORMYLATION AND REDUCTION', Organic Preparations and Procedures International, 10: 1, 29 — 32
To link to this Article: DOI: 10.1080/00304947809355001
URL: http://dx.doi.org/10.1080/00304947809355001

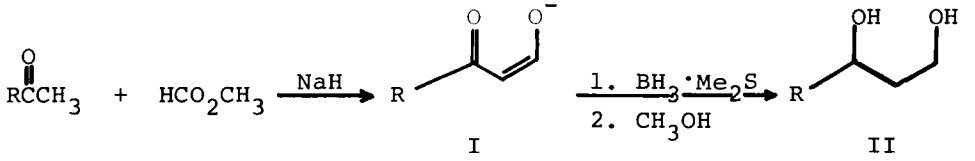
ORGANIC PREPARATIONS AND PROCEDURES INT. 10(1), 29-32 (1978)

1,3-PROPANEDIOLS FROM KETONES BY FORMYLATION AND REDUCTION

D. E. Pearson* and John D. Weaver†

Department of Chemistry, Vanderbilt University
Nashville, TN 37235

We report on improved variation in the synthesis of 1-monosubstituted-1,3-propanediols from methyl ketones. This method which presumably is also applicable to any carbonyl compound with an acidic α-proton, involves the addition of a formyl group to the α-carbon in ether and subsequent reduction of the sodium enolate salt with borane-methyl sulfide complex (BMS). The formylation step in this synthesis affords the enolate salt of a keto-aldehyde (I), which can serve as a precursor for 1,3-diols, β-ketoalcohols[1] and β-ketoamines.[2] Intermediate I also may be obtained from the same starting material by the Vilsmeir reaction.[3]



Of the previous techniques investigated for the preparation of I, the most successful is probably that of Corey and Cane,[1] which utilizes the ketone, sodium hydride and the formate ester in a 1:2:4 molar ratio in 1,2-dimethoxyethane (DME). Sodium hydride is superior to sodium ethoxide, because the former introduces no additional compound which must subsequently be removed. In addition, the findings of Remers *et al.*[4] and Rosenblum *et al.*[5] show that prolonged heating of the enolate adduct in the presence of a base such as ethoxide could result in the loss of the formyl group, pos-

sibly giving an acetylene. In view of these possibilities, we feel that Corey's choice of the high boiling DME as solvent might result in the heat-induced decomposition of the product. We have found that diethyl ether is the solvent of choice, primarily because of its ease of removal at or below room temperature under reduced pressure. Very little decomposition occurred from such treatment, and the product could be used without further purification. That decomposition is possible, was shown by the fact whereas a 79% yield of crude product was obtained from the reaction of pinacolone and methyl formate (R = t-Bu), the yield dropped to 19% after recrystallization from hot ethyl acetate-hexane; recrystallization from hot pentane-ether gave a 74% isolated yield.

Recently, a new versatile organoborane reagent, the borane-methyl sulfide complex, has been introduced for reduction[6,7] and hydroboration.[8] This complex (BMS) appears to be an attractive alternative to borane-THF and overcomes many of the disadvantages of the latter. In this study, it was observed that the formyl derivatives of several ketones were reduced to 1,3-diols by BMS in a much higher yield than by either sodium borohydride or sodium diethylaluminum hydride (OMH-1). The reduction with BMS can be performed at room temperature in THF or a variety of other solvents, and the fact that borane is a Lewis acid instead of a base as are LAH and $NaBH_4$ prevents formation and subsequent decomposition of the enolate before reduction occurs.

EXPERIMENTAL

Borane-methyl sulfide (BMS) was obtained from Aldrich Chemical Co. and was stored under N_2 in the refrigerator. All other reagents were purified in the normal way and dried over 4 Å molecular sieves. Melting points are corrected. Nmr spectra were obtained using a Varian EM-360 MHz spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tn.

Sodium Salt of α-Formylpinacolone (I, R = t-Bu).- Sodium hydride (50% dispersion in mineral oil; 5.1 g, 106 mmoles) was washed once with petroleum ether and mixed with 50 ml of dry ether. The slurry was cooled to 0° and a solution of methyl formate (12 ml, 200 mmoles) in 40 ml of ether was added. After several minutes, a solution of pinacolone (5.0 g, 50 mmoles) in 25 ml of ether was added dropwise. After 30 minutes, the ice bath was removed and the mixture was stirred at room temperature overnight. A small amount of excess sodium hydride was filtered from the solution and washed with ether (CAUTION!), and the combined filtrates were evaporated under reduced pressure at room temperature. The orange residue was taken up in hot pentane-ether, filtered, and slowly cooled to -78°. The enolate salt was obtained as a soft white powder. An additional quantity of the product was isolated by evaporation of the mother liquor to dryness, followed by washing of the residue with pentane until all the color had disappeared. The total yield was 5.5 g (74%), dec. 70°.

Nmr (D_2O): δ 1.00 (s, 9, CH_3), δ 8.90 (q, 2, -CH=CH-).

4,4-Dimethyl-1,3-pentanediol (II, R = t-Bu).- The formyl adduct I (5.4 g, 36 mmoles) was mixed with 100 ml of dry THF under N_2. A solution of BMS (10 ml, 100 mmoles) in 25 ml of THF was added at such a rate that the temperature did not rise above 40°. The reduction was allowed to proceed for 4 hrs. at 25°. After this time, 20 ml of anhydrous methanol was slowly added, followed after several minutes by the addition of 50 ml of 3 N sodium hydroxide. The organic phase was washed with saturated brine and dried (Na_2SO_4). The solvent was evaporated to afford 3.6 g (76%) of white powder, which was recrystallized from hexane, mp. 62-64°, lit.[9] mp. 65.5-66°.

Nmr ($CDCl_3$-D_2O): δ 0.88 (s, 9, CH_3), δ 1.60 (m, 2, CH_2 at position 2), δ 3.48 (q, 1, CH), δ 3.48 (t, 2, CH_2 at position 1). (The spectrum obtained in $CDCl_3$ without D_2O shows strong coupling between hydroxyl protons and ad-

jacent alkyl protons).

Anal. Calcd for $C_7H_{16}O_2$: C, 63.59; H, 12.20.

Found: C, 63.74; H, 12.04.

3-Phenyl-1,3-propanediol (II, R = Ph).- This compound was made similarly, giving a crude oil, 89%. It was purified by fractional elution[10] from silica gel by hexane and then by hexane-ethyl acetate. The properties of the product and the mp. of the bis-nitrobenzoate derivative compared favorably with those in the literature.[11]

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(Received September 17, 1977; in revised form November 21, 1977)