

AN IMPROVED SYNTHETIC PREPARATION OF 3-BUTENAL

Michael T. Crimmins,* Steven J. Kirincich, Angela J. Wells and Allison L. Choy

Venable and Kenan Laboratories of Chemistry
The University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599-3290

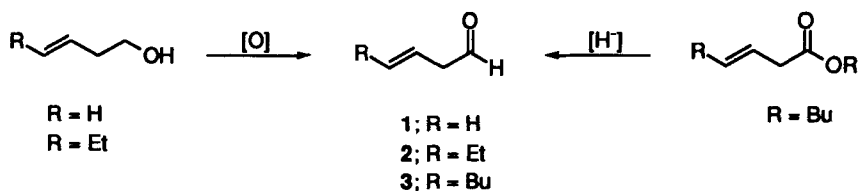
ABSTRACT: A convenient synthesis of 3-butenal from aqueous glyoxal and allyl bromide is described. The preparation readily provides multigram quantities of 3-butenal.

The asymmetric aldol reaction has become one of the most powerful tools available for the construction of carbon-carbon bonds and the assembly of polypropionate units.¹ Under suitable conditions, aldehydes of varying degree of structural and stereochemical complexity react with enolates in an efficient, predictable manner to provide hydroxyacids and their derivatives. Like all other organic transformations, the utility of the aldol reaction is heavily dependent on the cost and availability of reagents and starting materials.

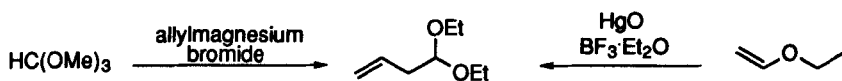
In the course of some recent synthetic efforts, we required gram quantities of a β,γ -unsaturated aldehyde such as 3-butenal **1**. Although the most straightforward approaches to 3-butenal or other suitable unsaturated aldehyde would involve either oxidation of a homoallylic alcohol² or reduction of a β,γ -unsaturated acid derivative,³ we were unable to implement these strategies to obtain

* To whom correspondence should be addressed.

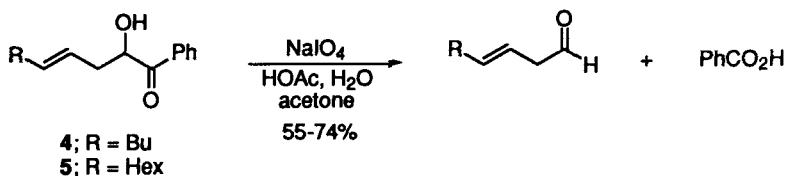
β,γ -unsaturated aldehydes in acceptable yields. An alternative method which involves the palladium-catalyzed formylation of allylic halides does not appear to be practical because of the use of specialized high pressure equipment.⁴



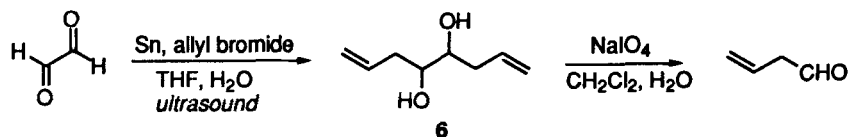
An expanded literature search uncovered two fundamentally different approaches to β,γ -unsaturated aldehydes. 1,1-Diethoxy-3-butene available from either the addition of allylmagnesium bromide to trimethylorthoformate⁵ or from the dimerization of ethyl vinyl ether,⁶ has been reported to undergo acid catalyzed hydrolysis to provide 3-butenal 1.⁷ While this protocol is effective, we have experienced considerable difficulty with the separation of the aldehyde from the ethanol byproduct.



An alternative method to β,γ -unsaturated aldehydes involves the formation and oxidative cleavage of vicinal diols. Oxidation of ene adduct **5** has been reported to provide easily purified aldehydes in 55-74% yield.⁸ A similar but more lengthy approach which utilizes a symmetric diol to provide 2 equivalents of aldehyde product was utilized by Oppolzer.⁹



In 1987, Einhorn and Luche described the reaction of aldehydes with allylic halides and either tin or zinc metal under aqueous conditions.¹⁰ In particular, the reaction of commercially available 40% aqueous glyoxal with allyl bromide in the presence of tin metal provided 1,7-octadiene-4,5-diol **6** in 51% yield. We have been able to achieve yields exceeding 80% for this reaction on 1 g scale. Subsequent treatment of the diol with sodium periodate in a dichloromethane-water biphasic system produced 3-butenal in excellent yield and high purity after atmospheric pressure distillation. We have found this two step procedure to be far superior to previous syntheses of 3-butenal on a practical level. 3-Butenal prepared by this method gave excellent yields in asymmetric aldol reactions with the chlorotitanium enolates of acyloxazolidinethiones.¹¹



Experimental Procedure:

1,7-octadiene-4,5-diol (6). To a three-neck flask equipped with a mechanical stirrer was added THF (130 mL) and H₂O (130 mL), 40% aqueous glyoxal (37.58 g 40% solution, 15.03 g glyoxal, 0.258 mol), granular 30 mesh tin metal (73.99 g, 0.623 mol), and allyl bromide (75.00 g, 0.620 mol). The solution was stirred and irradiated with ultrasound for 1.5 h. The resulting emulsion was concentrated to half volume in vacuo. A solution of 10 % HCl was added until the emulsion

separated into two phases. The resulting mixture was separated, the aqueous layer was washed several times with CH_2Cl_2 and the combined organic layers were washed with brine and concentrated. The crude 1,7-octadiene-4,5-diol product was purified by flash chromatography to give 18.81 g, 52% yield. ^1H NMR 2.0 - 2.40 (m, 6 H, CH_2CHOH), 3.45 - 3.78 (m, 2 H, CHCHOH), 5.0 - 5.23 (m, 4 H, $\text{CH}_2=\text{CH}$), 5.7 - 5.95 (m, 2 H, $\text{CH}_2=\text{CH}$).

3-butenal. 1,7-octadiene-4,5-diol (12.74 g, 0.090 mol) was dissolved in dichloromethane (100 mL) and H_2O (100 mL) and cooled to 0°C . NaIO_4 (19.250 g, 0.090 mol) was added to the mixture in portions. The mixture was allowed to warm to room temperature and stirred for 2.0-2.5 h. The layers were separated and the organic layer was washed with a small amount of water and brine and dried over Na_2SO_4 . Most of the CH_2Cl_2 was removed at atmospheric pressure with a jacketed Vigreux column and short path distillation head. Distillation was complete when ^1H NMR indicated the presence of 3-butenal the dichloromethane fractions. By ^1H NMR, 72% yield of 3-butenal as a solution (ca. 20% butenal by volume, ca. 15% by weight) in CH_2Cl_2 was produced. 3-butenal is stable as a CH_2Cl_2 solution when stored at -80°C . ^1H NMR 3.2 (m, 2 H, $\text{CH}_2\text{C}=\text{O}$), 5.3 (m, 1 H, $\text{CH}_2=\text{CH}$), 5.7 - 6.0 (m, 2 H, $\text{CH}_2=\text{CH}$), 9.7 (t, $J = 0.5$ Hz, 1 H, $\text{HC}=\text{O}$).

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