A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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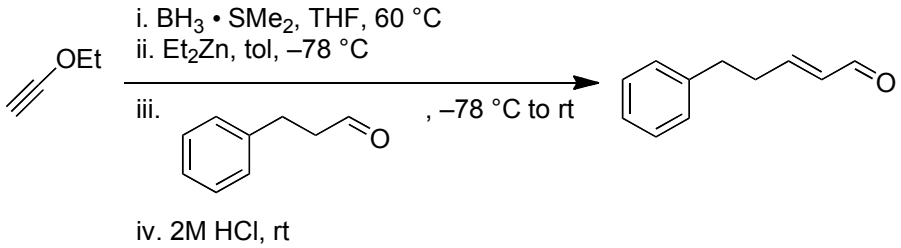
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Enals via a Simple Two-Carbon Homologation of Aldehydes and Ketones



Submitted by Petr Valenta, Natalie A. Drucker, and Patrick J. Walsh.[1]
Checked by David Hughes.

1. Procedure

CAUTION! Neat diethylzinc may ignite on exposure to air and reacts violently with water. It must be handled and reacted under nitrogen. The reaction solvent must be dried and distilled prior to use and all glassware and syringes must be thoroughly dried.

(E)-5-Phenylpent-2-enal. An oven-dried, 1-L, 3-necked round-bottomed flask containing a 3-cm oval PTFE-coated magnetic stir bar is equipped with a nitrogen inlet adapter and two rubber septa, one of which is pierced with a thermocouple probe (Note 1). The flask is charged with a 50 wt % solution of ethoxyacetylene in hexanes (22 mL, 16.8 g, 0.12 mol, 1.8 equiv) (Note 2) and THF (70 mL), then cooled to 2 °C in an ice-bath. With stirring, 2M borane dimethyl sulfide complex in THF (17.5 mL, 35 mmol, 0.5 equiv) is added dropwise via a 30 mL syringe over 30 min, keeping the temperature below 7 °C. The reaction mixture is stirred for 1 h at 2 °C (Note 3), then the ice-bath is replaced with a heating mantle. The nitrogen adapter is replaced with a vacuum-distillation head connected to a 500-mL round bottom flask immersed in a dry-ice bath. The volatile materials are removed at reduced pressure (60 mmHg) by applying gentle heating to the reaction flask (Note 4). After removal of volatile materials, the reaction flask is back-filled with nitrogen and the brown oil is dissolved by addition of toluene (65 mL) (Note 5). The stirred solution is cooled to –75 °C in a dry ice/acetone bath and 1.1M diethylzinc in toluene (96 mL,

105 mmol, 1.5 equiv) (Note 6) is added by cannula over 10 min, keeping the temperature below –65 °C. After the solution is stirred for 30 min between –70 and –75 °C, hydrocinnamaldehyde (9.1 g, 68 mmol, 1.0 equiv) (Note 7) is added dropwise via a 20 mL syringe over 2 min. The mixture is allowed to warm to 20 °C over 1 h and stirred for 3 h (Note 8). The reaction is then cooled to 5 °C in an ice-bath and *t*-butyl methyl ether (100 mL) is added. The nitrogen gas adapter is replaced with a 300-mL addition funnel. Vigorous stirring of the reaction mixture is commenced and water (100 mL) is carefully added over 5 min, keeping the temperature below 20 °C. Gas (ethane) is evolved and a white precipitate of zinc oxide is formed. The ice bath is removed and aqueous 2M HCl (200 mL) is added over 5 min via the addition funnel. The reaction mixture is stirred for 20 min until the white precipitate of zinc oxide dissolves (Note 9). The quenched reaction mixture is transferred to a 1-L separatory funnel. The aqueous layer is separated and back-extracted with MTBE (100 mL). The combined organic layer is washed with saturated aqueous sodium bicarbonate (200 mL) and brine (50 mL), then dried by filtration through 50 g sodium sulfate. The volatile materials are removed by rotary evaporation (40 °C bath temperature, 60 mmHg) to afford 12 g of a brown oil. The crude product is purified by flash column chromatography (Note 10) and concentrated by rotary evaporation (40 °C bath temperature, 60 mmHg) to afford 7.7–8.2 g (71–75 % yield) as a pale yellow oil (Notes 11 and 12).

2. Notes

1. The internal temperature was monitored using a J-Kem Gemini digital thermometer with a Teflon-coated T-Type thermocouple probe (12-inch length, 1/8 inch outer diameter, temperature range –200 to +250 °C).

2. The following reagents and solvents were used as received: ethoxyacetylene (GFC Chemicals, 50 wt % solution in hexanes), tetrahydrofuran (Sigma-Aldrich, 99.9%, inhibitor-free, Sure-Seal® bottle), 2M borane dimethyl sulfide in THF (Sigma-Aldrich), 15 wt % diethylzinc in toluene (1.1M, Sigma-Aldrich), toluene (Sigma-Aldrich, Chromasolv, 99.9%, anhydrous, Sure-Seal® bottle), hexanes (Fisher, ACS reagent, >98.5%), t-butyl methyl ether (>98.5%, Sigma-Aldrich), ethyl acetate (Fisher, ACS reagent, >99%), 2N HCl (Fisher), and silica gel (Fisher, 230-400 mesh, 60 Å). Deionized water was used throughout.

3. The conversion of ethoxyacetylene to tris(ethoxyvinyl)borane (Scheme 1) was followed by NMR by diluting a 0.05 mL reaction aliquot in 0.6 mL THF-d_8. Diagnostic signals for ^{1}H NMR were δ 4.05 (q, 2H) for ethoxyacetylene and 3.84 (q, 6H) for tris(ethoxyvinyl)borane; ^{13}C NMR diagnostic signals were δ 74.9 and 91.5 for ethoxyacetylene and 65.3 and 163.6 for tris(ethoxyvinyl)borane. The reaction was complete within 10 min after addition of borane dimethyl sulfide. The 20% excess charge of ethoxyacetylene was reflected in its constant level in samples taken between 10 min and 1 h after addition of borane dimethyl sulfide. The tris(ethoxyvinyl)borane was about 90% pure after concentration based on NMR analysis. Tris(ethoxyvinyl)borane has the following spectroscopic properties: ^{1}H NMR (500 MHz, THF-d_8. ref 3.57) δ: 1.23 (t, J = 7.0 Hz, 9 H), 3.84 (q, J = 7.0 Hz, 6 H), 5.30 (d, J = 13.9 Hz, 3 H), 7.06 (d, J = 13.9 Hz, 3 H); ^{13}C NMR (125 MHz, THF-d_8. ref 67.57) δ: 15.2, 65.3, 104.2 (br), 163.6.

4. Contact of the reaction mixture with air was avoided at all times to avoid air oxidation of the borane intermediate. A dry ice/acetone cold trap was placed between the receiver flask and vacuum line to ensure dimethyl sulfide was fully trapped. The volatile materials were distilled under a vacuum of 60 mmHg, with most of the material distilling at a pot temperature of –2 to +2 °C. The heating mantle was removed when the pot temperature rose to 10°C, then vacuum was applied for an additional hour as the contents warmed to ambient temperature, ensuring complete removal of volatile materials.

5. Toluene was added in two portions via a 50-mL syringe from a fresh Sure-Seal® bottle.

6. The 1.1M diethylzinc in toluene solution was transferred by cannula from a 100 g bottle via an 18-gauge needle by application of slight nitrogen pressure to the bottle. About 90% of the contents were transferred; the bottle was weighed before and after addition to obtain the exact amount added (density = 0.91 g/L).

7. The checkers purchased hydrocinnamaldehyde from Acros (labeled as 95%, GC indicated 93.5%). The aldehyde (40 g) was distilled at 60 mmHg through a 10 cm Vigreaux column, collecting a center cut of 25 g (62%) boiling at 140–143 °C which was stored in the freezer. Purity by GC: 97.5% (t_R = 8.4 min; conditions: Agilent DB35MS column; 30 m x 0.25 mm; initial temp 60 °C, ramp at 20 °C/min to 280 °C, hold 15 min). The submitters purchased 90% technical grade hydrocinnamaldehyde from

Sigma-Aldrich, which was distilled under reduced pressure (100 °C, 13 mmHg) and stored under nitrogen in the glove box.

8. The reaction was followed by ^{1}H NMR of a reaction aliquot that was worked up as follows. A 0.1 mL sample was quenched into a vial containing 1 mL MTBE and 1 mL of 2N HCl. The sample was vigorously shaken and allowed to stand for 15 min. The MTBE layer was separated and evaporated, then dissolved in $CDCl_3$ for ^{1}H NMR analysis. The aldehyde protons were diagnostic at δ 9.51 (doublet) for the product and 9.85 (triplet) for hydrocinnamaldehyde. The reaction typically proceeds to >98% conversion. Hydrocinnamaldehyde elutes with an R_f very similar to the product (0.45 product, 0.47 hydrocinnamaldehyde using 20% EtOAc/hexanes, EMD silica gel 60 F254, 2.5 x 7.5 cm plates), so following the reaction by TLC is difficult.

9. The pH of the resulting aqueous layer should be less than 3 to effect complete hydrolysis. If necessary, an additional 20 mL of 2M HCl should be added.

10. Flash column chromatography was performed with 400 g silica gel wet-packed with 5% EtOAc/hexanes and topped with 1 cm sand. The crude product was diluted with 10 mL of dichloromethane to load onto the column. Approximately 3 L of 7 % EtOAc/hexanes was used as eluent, flow 50 mL/min, collecting 50 mL fractions. Product eluting in fractions 40-55 were combined and concentrated by rotary evaporation (40 °C, 60 mmHg), then held under vacuum (60 mmHg) for 2 h at room temperature to afford product as a pale yellow oil. The chromatography was followed by TLC using PMA detection (R_f = 0.45 in 20% EtOAc/hexanes). Product elution could also be followed by UV detection, but this method is not recommended since several non-UV active impurities elute just prior to product elution.

11. The submitters used a 2M solution of diethylzinc prepared by adding neat diethylzinc to toluene in a glovebox. The submitters also prepared fresh 1 M borane-dimethylsulfide complex by adding neat borane-dimethylsulfide complex to THF. The submitters reported a yield of 79 % with a GC product purity of 92 %.

12. (*E*)-5-Phenylpent-2-enal has the following physical and spectroscopic properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.66–2.71 (m, 2H), 2.85 (t, J = 7.5 Hz, 2 H), 6.15 (ddt, J = 15.8, 7.8, 1.4 Hz, 1 H), 6.87 (td, J = 15.7, 6.7 Hz, 1 H), 7.20–7.25 (m, 3 H), 7.31–7.34 (m, 2 H), 9.51 (d, J = 7.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.3, 34.4, 126.6, 128.5, 128.8, 133.6, 140.4,

157.4, 194.1. IR (neat) cm^{-1}: 3064, 3031, 2930, 1685, 1490, 1120. HRMS calcd. for $C_{11}H_{12}O$ (MH^+): 161.0966, found 161.0964. GC-MS (EI) *m/z* (relative intensity), 160 (8%, M^+), 142 (14%), 129 (12%), 116 (75%), 92 (35%), 91 (100%), 77 (18%), 65 (60%), 51 (21%). Purity by GC: 97% (t_R = 10.5 min; conditions same as in Note 7). The material crystallizes in the freezer and has an approximate melting point of –12 to –14 °C.

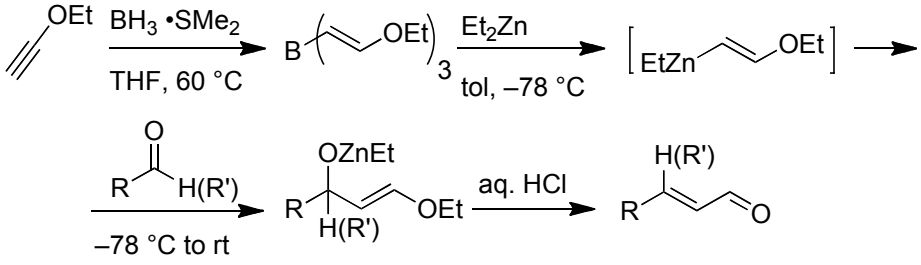
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

3. Discussion

α,β-Unsaturated aldehydes continue to attract wide-spread interest for their utility in organic synthesis,[2] organocatalysis,[3] and biochemistry.[4] Many existing approaches to synthesize enals are based on two-carbon homologation of aldehydes.[5] Reactions of aldehydes with various Wittig,[6] Horner-Emmons[7] and Peterson-type[8] reagents and with enolate of acetaldehyde[9] suffer from strongly basic reaction conditions. Such reaction conditions often result in self-condensation, destruction of base-sensitive functionalities and racemization of *α*-stereocenters via deprotonation. Basic conditions can be avoided by use of *C*-silylated imines[10] or alkoxyvinyl zirconium species,[11] which are prohibitively expensive or labor intensive reagents.

Scheme 1. Two-carbon homologation of aldehydes and ketones

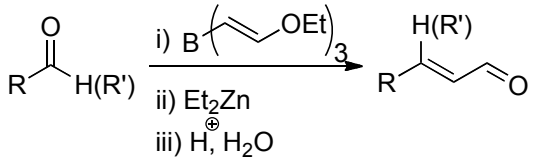


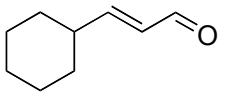
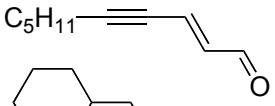
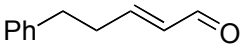
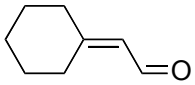
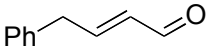
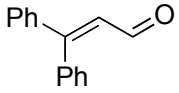
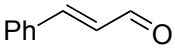
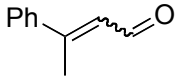
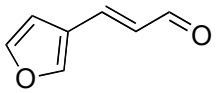
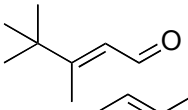
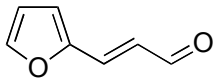
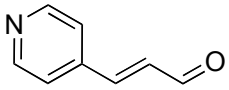
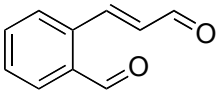
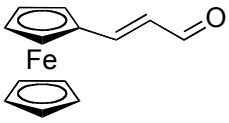
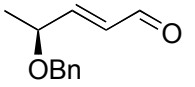
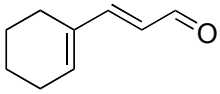
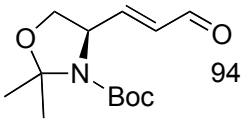
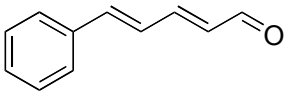
Our method utilizes only common commercially available chemicals and avoids the use of strong bases (Scheme 1).[12] The two-carbon

homologation of aldehydes and ketones involves hydroboration of ethoxyacetylene with borane-dimethyl sulfide complex followed by transmetallation of the resulting vinylboron intermediate to zinc using diethylzinc. The resulting ethoxy-vinyl zinc species adds to aldehydes and ketones to generate allylic zinc alkoxides. Protonation with aqueous acid results in elimination of water and generation of desired enal.

The broad substrate scope of the reaction is presented in Table 1. Two-carbon homologation of aliphatic (Table 1, entries 1 to 3), aromatic (entries 4 and 8), heteroaromatic (entries 5 to 7), α,β-unsaturated (entries 9 and 10), propargylic aldehydes (entry 11), and dialdehydes (entries 16 and 17) was achieved with high isolated yields. Ketones were also successfully homologated (entries 12 to 15). Reaction with unsymmetrical ketones resulted in mixtures of *E*/*Z* isomers (entry 14). When the substituents are very different in size (*t*-butyl vs. methyl) *E*/*Z* ratios up to 15:1 occurred (entry 15). *o*-Phthalaldehyde was homologated only once due to intramolecular formation of a hemiacetal, preventing the reaction with the second aldehyde (entry 17). No racemization of α-chiral aldehydes was observed under these conditions (entries 18 and 19). Isolated yields of volatile enals can be improved by use of hexanes instead of toluene as solvent, minimizing product lost during final evaporation of solvents.

Table 1. Substrate scope of two-carbon homologation of aldehydes and ketones



Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1		94	11		87
2		94	12		86
3		89	13		54
4		96	14		83[b]
5		92	15		53[c]
6		91	16		70
7		72	17		54
8		93	18		88 (98%$_{ee}$)[d]
9		95	19		94 (98%$_{ee}$)[d]
10		95			

[a] Isolated yield. [b] *E*:*Z* = 3:1. [c] *E*:*Z* = 15:1. [d] *ee* detemined by HPLC

1. P. Roy and Diana T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, pwalsh@sas.upenn.edu. PJW thanks the NSF for support of this work.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethoxyacetylene: Ethyne, ethoxy-; (927-80-0)
Borane dimethyl sulfide complex: Boron, trihydro[thiobis[methane]]-; (13292-87-0)
Diethyl zinc: Zinc, diethyl-; (557-20-0)
Hydrocinnamaldehyde: Benzenepropanal; (104-53-0)
5-Phenyl-pent-2-enal: 2-Pentenal, 5-phenyl-, (2E)-; (37868-70-5)

Patrick J. Walsh received his B.A. from UC San Diego (1986) and Ph.D. in organometallic chemistry with Prof. Robert G. Bergman at UC Berkeley (1991). He was an NSF postdoctoral fellow with Prof. K. B. Sharpless at the Scripps Research Institute. Walsh became an assistant professor at San Diego State University in 1994 and from 1996-1999 was also a professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana (Mexico). In 1999 he moved to his current position at the University of Pennsylvania where he holds the Alan G. MacDiarmid Chair. Walsh's interests are in asymmetric catalysis, development of new methods, reaction mechanisms, and inorganic synthesis. With Prof. Marisa Kozlowski Walsh wrote *Fundamentals of Asymmetric Catalysis*.

Petr Valenta was born in Plzen, Czech Republic. He received his M.S. in Chemistry from University of Pardubice, where he performed undergraduate research with Professor Milos Sedlak. As an Alfred Bader fellow, Petr obtained his Ph.D. from University of Pennsylvania in 2010. In research group of Professor Patrick J. Walsh he studied catalytic enantioselective reactions of hetero-vinyl zinc Reagents. Petr is currently a Research Chemist at Milliken and Company in Spartanburg, SC.

Natalie A. Drucker was born in 1988 and was raised in Hollywood, Florida. She graduated with a B.A. in Chemistry from University of Pennsylvania, where she worked in the laboratory of Professor Patrick J. Walsh. She currently studies at University of Florida College of Medicine.