A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

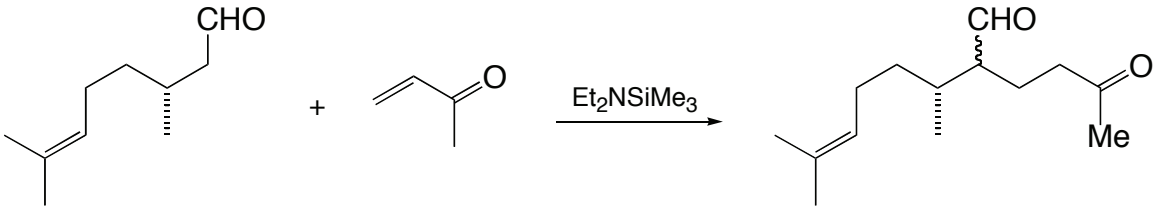
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

DOI:10.15227/orgsyn.080.0195
Organic Syntheses, Vol. 80, p. 195-199 (2003); Coll. Vol. 11, p. 416-419 (2009).

DIETHYLAMINOTRIMETHYLSILANE-CATALYZED 1,4-ADDITION OF ALDEHYDES TO VINYL KETONES: (3*R*)-3,7-DIMETHYL-2-(3-OXOBUTYL)-6-OCTENAL
[(6-Octenal, 3,7-dimethyl-2-(3-oxobutyl)-, (3*R*)-)]



Submitted by Hisahiro Hagiwara, Hiroki Ono, and Takashi Hoshi.[1]
Checked by Kwame Nti-Addae and Steven Wolff.

1. Procedure

(3R)-3,7-Dimethyl-2-(3-oxobutyl)-6-octenal. To a two-necked, 300-mL flask, equipped with a magnetic stirrer, addition funnel, and condenser with a nitrogen balloon on the top, and immersed in an ice-cooled bath is added 18.1 mL of citronellal (100 mmol) (Note 1), 12.5 mL of 3-buten-2-one (150 mmol) (Note 2), 1.9 mL of diethylaminotrimethylsilane (10 mmol) (Notes 3, 4) and 400 mL of acetonitrile (Note 5). Following the addition, the resulting homogeneous solution is heated at reflux in an oil bath and the progress of the reaction is monitored by TLC analysis of the product using Merck silica gel 60 F_{254} plates: $R_f = 0.39$ (5:1 hexane:ethyl acetate). After 46 h, when the citronellal has been consumed, the resulting solution is concentrated to dryness under reduced pressure and the residue is distilled using a Kugelrohr apparatus twice (oven temperature 120~140 °C at 1.9 mm) to give (3*R*)-3,7-dimethyl-2-(3-oxobutyl)-6-octenal (21.6 g, 96%) (Notes 6-8) as a pale yellow liquid.

2. Notes

1. *R*-(+)-Citronellal was obtained from Tokyo Chemical Industry Co. Ltd. and used as received.

2. 3-Buten-2-one was obtained from Merck & Co., Inc. and used as received.

3. Diethylaminotrimethylsilane was obtained from Shin-Etsu Chemical Co., Ltd. and used as received.

4. Diethylaminotrimethylsilane can be prepared according to the procedure by Middleton, W. J.; Bingham, E. M. *Org. Synth., Coll. Vol. VI,* **1988**, 440.

5. Acetonitrile (Kanto Chemical Co., Ltd. special grade) was used as received.

6. The purity of the product was determined to be 100% by medium pressure LC (silica gel packed column, eluent: 5:1 n-hexane:ethyl acetate).

7. The physical properties of (3*R*)-3,7-dimethyl-2-(3-oxobutyl)-6-octenal, a 1:1 mixture of diastereoisomers, are as follows: IR (thin film) cm^{-1}: 2930, 2709, 1722, 1450, 1376, 1240 and 1164; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.89 (d, 1.5 H, J = 6.9), 0.99 (d, 1.5 H, J = 6.9), 1.60 (s, 3 H), 1.69 (s, 3 H), 1.08-2.10 (m, 7 H), 2.13 (s, 3 H), 2.26-2.65 (m, 3 H), 5.08 (m, 1 H), 9.60 (d, 0.5 H, J = 2.4) and 9.64 (0.5 H, J = 2.9); ^{13}C (50 MHz) δ: 15.9, 16.7, 17.6, 18.0, 19.7, 25.1, 25.6, 29.9, 32.2, 33.3, 33.8, 34.4, 41.36, 41.42, 55.9, 56.2, 123.7, 131.9, 204.9, 205.2, 207.9 and 208.0; m/z 224 (M^+, 0.1%), 148 (32), 109 (26), 95 (38), 82 (32), 71 (25), 69 (52), 58 (28), 55 (37), 43 (100) and 41 (68); Calcd for $C_{14}H_{24}O_2$; M^+, 224.1776. Found: M^+, 224.1798.

8. When 0.5 eq of Et_2NTMS was used, the reaction is complete in 19 h in 100% yield as shown in the Table, entry 8.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This is a mild, simple and practical procedure for 1,4-addition of an aldehyde to methyl vinyl ketone,[2] without converting the aldehyde into an enamine or a silyl enol ether. The products, substituted 5-ketoaldehydes, are

important compounds, especially for the preparation of substituted 2-cyclohexen-1-one derivatives, which have been versatile starting materials for syntheses of natural products such as terpenoids.[3] These 5-ketoaldehydes have been prepared previously by the 1,4-addition of modified aldehydes, i.e., morpholinoenamines of aldehydes,[4,5] trimethylsilyl enol ethers of aldehydes in the presence of a Lewis acid,[6] or diethylallylamine in the presence of a catalytic amount of a Ru complex,[7] to methyl vinyl ketones.

The reaction is carried out simply by refluxing an acetonitrile solution of the aldehyde, vinyl ketone and 10 mol% of diethylaminotrimethylsilane until disappearance of the aldehyde (monitored by TLC analysis). Bulb-to-bulb distillation provides the 5-ketoaldehydes without aqueous work up. When the amount of diethylaminotrimethylsilane is increased, the reaction proceeds faster (Table, entry 8), although the resulting reaction mixture is not colorless. Some representative examples of the present reaction are shown in the Table. The mildness of the reaction is well exemplified by obtaining satisfactory yields in the reactions with acid- or base-sensitive aldehydes (having a THP or acetyl protecting group) (Table, entries 4 and 5).

The reaction also can be carried out without solvent, although the yields using isobutyraldehyde and citronellal were relatively low.

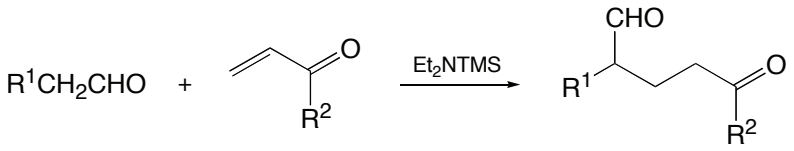
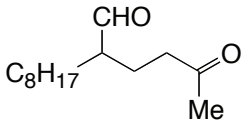
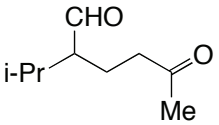
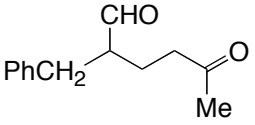
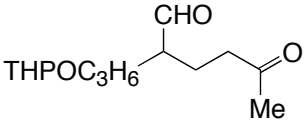
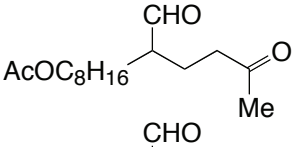
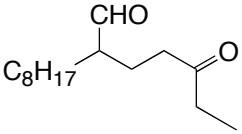
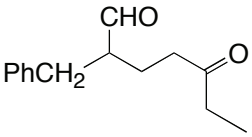
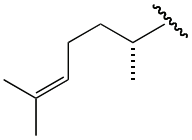
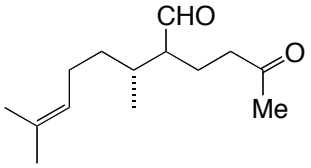


Table 1,4-Addition of aldehydes with vinyl ketones

Entry	Aldehyde (R^1)	Vinyl ketone (R^2)	Time (hr)	Product	Isolated yield (%)
1	C_8H_{17}	Me	20		78
2	i-Pr	Me	9		64
3	$PhCH_2$	Me	6		59
4	$THPOC_3H_6$	Me	6		89
5	$AcOC_8H_{16}$	Me	9		76
6	C_8H_{17}	Et	10.5		76
7	$PhCH_2$	Et	4		68
8[a]		Me	19		100

[a]Et_2NTMS (0.5 equiv.) was used.

1. Graduate School of Science and Technology, Niigata University, 8050, 2-Nocho, Ikarashi, Nishi-ku, Niigata 950-2181, Japan.
2. Hagiwara, H.; Kato, M. *Tetrahedron Lett.* **1996**, *37*, 5139; Hagiwara, H.; Komatsubara, N.; Ono, H.; Okabe, T.; Hoshi, T.; Suzuki, T.; Ando, M.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 316.
3. Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 895.
4. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
5. Brown, M. *J. Org. Chem.* **1968**, *33*, 162.
6. Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777.
7. Nakajima, T.; Maruyama, Y.; Shimizu, I. In "Abstracts of Papers of 65th Annual Meeting of Chemical Society of Japan," Tokyo, **1993**; Vol. II, p. 335.

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

(3*R*)-3,7-Dimethyl-2-(2-oxobutyl)-6-octenal: 6-Octenal, 3,7-dimethyl-2-(3-oxobutyl)-, (3*R*)- (9); (131308-24-2)

R-(+)-Citronellal: 6-Octenal, 3,7-dimethyl-, (3R)- (9); (2385-77-5)

Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)

Diethylaminotrimethylsilane: Silanamine, *N,N*-diethyl-1,1,1-trimethyl- (9); (996-50-9)