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.

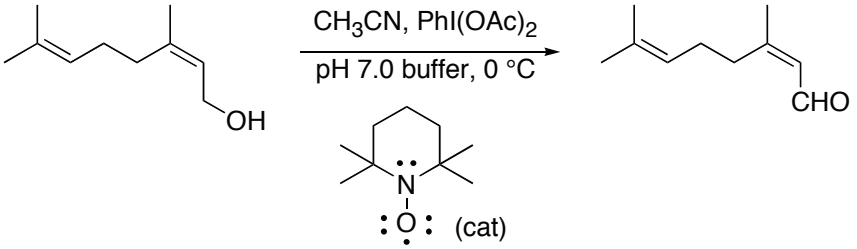
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.083.0018
Organic Syntheses, Vol. 83, p. 18-23 (2006); Coll. Vol. 11, p. 77-81 (2009).

OXIDATION OF NEROL TO NERAL WITH IODOBENZENE AND TEMPO
[(*Z*)-3,7-Dimethyl-2,6-octadienal]



Submitted by Giovanni Piancatelli and Francesca Leonelli.[1a]
Checked by Nga Do and John Ragan.[1b]
Discussion Addendum *Org. Synth.* **2012**, *89*, 311

1. Procedure

(Z)-3,7-Dimethyl-2,6-octadienal. A 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with the following order of the reagents: acetonitrile (28 mL) (Note 1), (*Z*)-3,7-dimethyl-2,6-octadien-1-ol (nerol) (5.70 mL, 32.5 mmol) (Note 2), aqueous pH 7.0 buffer solution (8 mL) (Note 3), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (490 mg, 3.24 mmol) (Note 4), and iodobenzene diacetate (IBD) (11.49 g, 35.71 mmol) (Note 5). The reaction mixture is stirred at 0 °C (Note 6) until nerol is no longer detectable by TLC analysis (Note 7). The reaction mixture is diluted with diethyl ether (100 mL) and transferred to a 500-mL separatory funnel. The orange mixture is washed with saturated aqueous sodium thiosulfate (2 x 50 mL) (Note 8). The aqueous phase is separated and extracted with diethyl ether (3 x 35 mL). The combined organic layers are washed with saturated aqueous sodium hydrogen carbonate (40 mL) and then with saturated aqueous sodium chloride (40 mL) (Note 9). The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator (35 °C, 70 mmHg). The residue is purified by column chromatography on silica gel (Note 10), using a 1:9 mixture of diethyl ether and hexanes as eluent (Note 11) to afford 4.30–4.39 g (87–89%) of (*Z*)-3,7-dimethyl-2,6-octadien-1-al (neral) as a colorless oil (Note 12). The material is homogenous by TLC, IR, ^{1}H and ^{13}C-NMR (Note 13).

2. Notes

1. "RPE-For analysis"-grade CH_3CN, as supplied by Carlo Erba Reagents (Italy), was used.

2. Nerol (97%) was purchased from Aldrich and used directly without purification. The compound revealed traces of geraniol (< 3%) from GCMS analysis (Shimadzu GCMS-QP5000; EQUITY^{TM}-5 FUSED SILICA Capillary Column 30 m x 0.32 mm x 0.25 μm film thickness; 80 °C (1 min), 80-240 °C (16 min), 240 °C (1 min)); t_{nerol} = 8.43, $t_{rgeraniol}$ = 8.75. The checkers used an Agilent HP-5 fused silica capillary column, 30 m x 0.32 mm x 0.25 μm; 250 ^{o}C detector, 100 ^{o}C isothermal program at 2 mL/min. This system gave the following retention times: t_{nerol} = 7.3 min, t_{neral} = 7.8 min, $t_{geraniol}$ = 8.4 min, $t_{geranial}$ = 9.1 min. The checkers' lot of nerol (also purchased from Aldrich) showed <0.5% geraniol contamination.

3. The pH 7.0 buffer solution was purchased from Fluka.

4. TEMPO (98%) was purchased from Aldrich and used as received.

5. IBD (98%) was purchased from Aldrich and used as received.

6. An ice-bath is placed under the reaction flask after the dissolution of IBD (≈ 3 min) because the reaction is slightly exothermic. On a smaller scale (1-5 mmol) this precaution is not necessary. The checkers placed the reaction flask in an ice bath prior to addition of the TEMPO and IBD; as the IBD began dissolving, an internal temperature probe showed a temperature rise of 6−9 °C over the course of the reaction. This was not an issue on the scale run, but should be carefully monitored if the reaction were to be significantly increased in scale.

7. The oxidation reaction is usually very fast and is complete after 20 min on the scale described above. The reaction was checked by TLC to confirm completion. Thin-layer chromatography analysis was carried out on E.Merck silica gel F254 plates by elution with Et_2O/hexanes (3/7), then sprayed with 2 N H_2SO_4 solution and heated with a hot plate for 1 min. The alcohol starting material has an R_f = 0.29 (light brown) and the aldehyde product has an R_f = 0.66 (deep purple). The reaction can also be monitored by GC/MS, as indicated by the checkers in Note 3.

8. Washing with saturated aqueous sodium thiosulfate removes TEMPO from the organic phase that becomes light yellow. If the organic phase should be still orange after the two washings, the solution is shaken in

the separatory funnel with 50 mL of saturated aqueous sodium thiosulfate and 15 mL of 0.5 N HCl until it becomes light yellow (the checkers found this extra thiosulfate-HCl wash to be necessary). TEMPO must be removed carefully at this stage, because it cannot be removed in the chromatographic purification.

9. The aqueous phase must be neutral. Acidic impurities can catalyze (*E*)/(Z) isomerization of the aldehyde in the purification stage.

10. Silica gel 60 (0.063-0.2 mm/ 70-230 mesh ASTM), purchased from Macherey-Nagel, was used. The column chromatography was performed using a 1/20 ratio between the crude product and silica gel.

11. The solvent required for the purification of the product varies from 1.4 to 1.6 L. The chromatographic solvent is removed with a rotary evaporator (35 °C, 70 mmHg).

12. The checkers used diethyl ether:hexane (2:8) for column elution. Attempted purification by distillation (bp 118–120 °C, 20 mmHg) led to significant olefin isomerization (the pot residue was a 50:50 mixture of neral and geranial).

13. The following analytical data have been obtained for (*Z*)-3,7-dimethyl-2,6-octadien-1-al: IR ($CHCl_3$) cm^{-1}: 1675 (C=O), 1635 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.58 (s, 3 H). 1.67 (s, 3 H), 1.97 (d, J = 1.2 Hz, 3 H), 2.15−2.25 (m, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 5.06−5.11 (m, 1 H), 5.86 (d, J = 8.3 Hz, 1 H), 9.88 (d, J = 8.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 25.3, 25.9, 27.2, 32.7, 122.4, 128.8, 133.9, 164.1, 191.0; GCMS purity >97%, t_r=8.56. The compound revealed traces of geranial (< 3%, t_r=8.98) from GCMS analysis (See Note 3).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

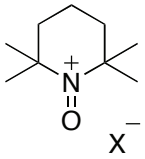
3. Discussion

The catalytic procedure described here illustrates a fast and inexpensive conversion of a (*Z*)-configured primary allylic alcohol into the corresponding (*Z*)-configured α,β-unsaturated aldehyde in high yields. The

result demonstrates the chemoselectivity of the process, in that the easily isomerizable *Z*-configuration of the nerol is maintained.

Various methods for the oxidation of nerol to neral are available. Although individually having some synthetic advantages, most methods suffer from one or more experimental drawbacks, such as severe or delicate reaction conditions, complicated reaction procedures, and the need to use toxic or unstable reagents.[2]

Oxammonium salts **1** are the effective oxidant species derived from TEMPO, and have been used extensively either in stoichiometric or in catalytic amounts for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds.[3] Compound **1** has been generated *in situ* from nitroxyl radicals, such as TEMPO, in combination with a number of secondary oxidants.[4]

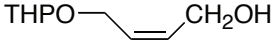
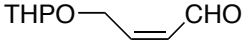
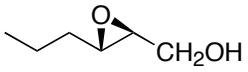
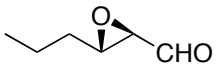
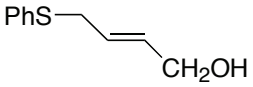
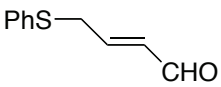
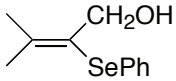
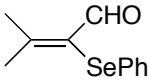
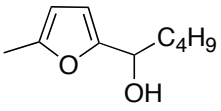
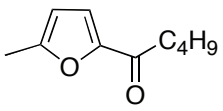


1

Hypervalent iodine reagents have been used recently for a variety of organic transformations.[4] *Inter alia*, IBD in combination with catalytic amounts of TEMPO is used as a stoichiometric oxidant in the conversion of primary and secondary alcohols to carbonyl compounds.[5] This oxidation protocol works efficiently at room temperature in dichloromethane (and also in most common organic solvents and neat in some cases) and can be performed in an open flask without special precautions (*e.g.* inert atmosphere or dry solvent). This process exhibits a very high degree of selectivity for the oxidation of primary alcohols to aldehydes, without noticeable over-oxidation to carboxyl compounds, and a high chemoselectivity in the presence of either secondary alcohols or of other oxidizable moieties.[5]

Many sensitive protective groups are not affected by this method. Some examples of carbonyl compounds synthesized with this method are reported in Table 1.[5]

Table 1. Oxidation of Primary Alcohols to Aldehydes[5]

Entry	Substrate	Product	Time (h)	yield (%)
1			0.2	95
2			1	70
3			1	70
4			15	55
5			3	95

1. (a) Dipartimento di Chimica, Università "La Sapienza", Piazzale Aldo Moro 5, 00185 Roma, Italy. (b) Chemical Research & Development, Pfizer Global Research & Development, Eastern Point Road, Groton, CT, USA.
2. For example, see: (a) Takahashi, M.; Oshima, K.; Matsubara, S. *Tetrahedron Lett.* **2003**, *44*, 9201-9203. (b) Matsuo, J-i.; Iida, D.; Yamanaka, H; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739-6750. (c) Bhar, S.; Chaudhuri, S. K. *Tetrahedron* **2003**, *59*, 3493-3498. (d) Matano, Y.; Nomura, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3028-3031. (e) Muldoon, J.; Brown, S. N. *Org. Lett*. **2002**, *4*, 1043-1045. (f) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041-3043. (g) Kakiuchi, N.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620-6625.
3. For recent reviews of TEMPO-catalyzed alcohol oxidation, see: (a) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153-1174. (b) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499-3548. (c) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774-781.
4. For recent reviews, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123-1178. (b) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627-630. (c) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis, Academic Press, San Diego*, **1997**. (d) Ochiai, M. in *Chemistry in Hypervalent Compounds* (Ed.: K. Akiba), Wiley-VCH, New York, **1999**, chap. 12. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523-2584. (f) Moriarty, R. *J. Org. Chem.* **2005**, *70*, 2893-2903.
5. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974 -6977.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(*Z*)-3,7-Dimethyl-2,6-octadien-1-ol (nerol); (106-25-2)

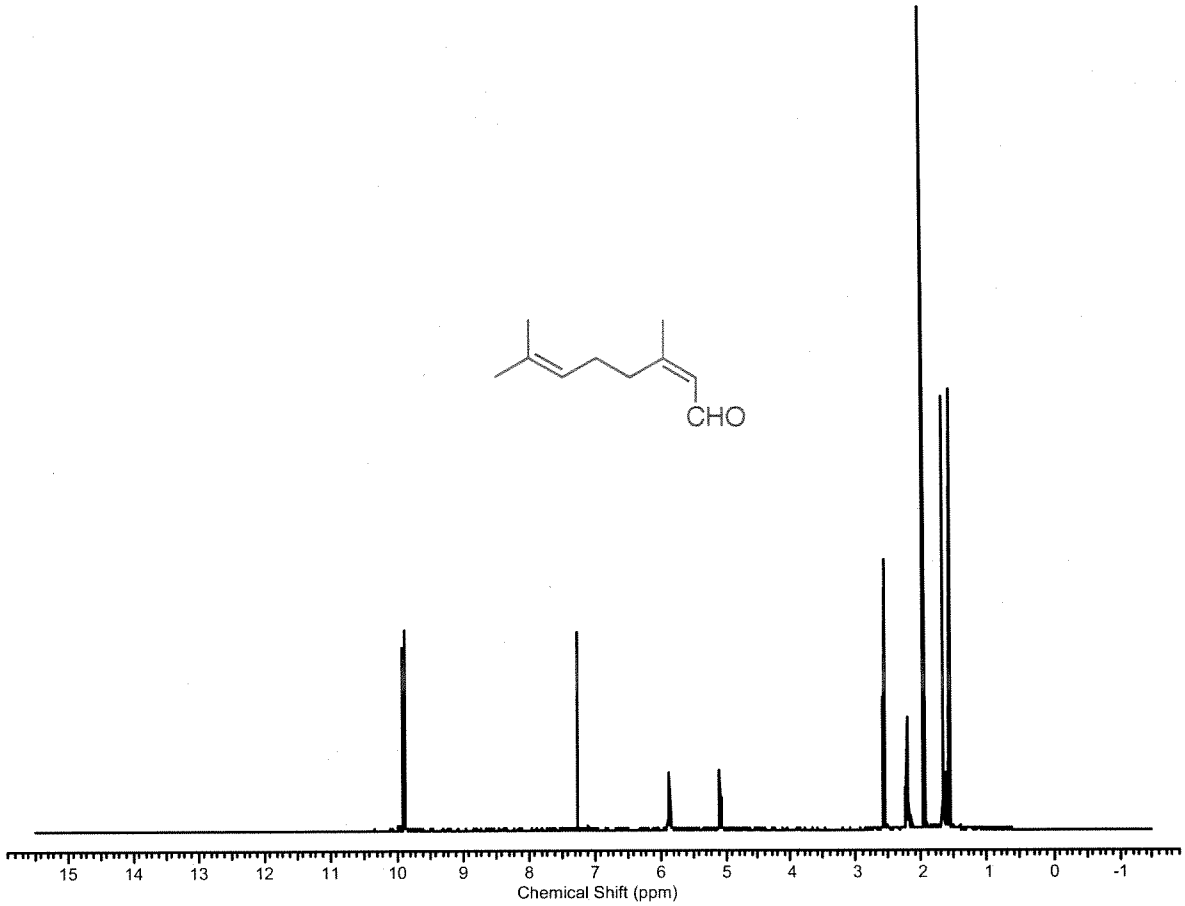
2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO): 2,2,6,6-Tetramethyl-1-piperidinyloxy; (2564-83-2)

Iodobenzene diacetate (IBD): Bis(acetato-κO)phenyliodine; (3240-34-4)

(*Z*)-3,7-Dimethyl-2,6-octadien-1-al (neral): (2Z)-3,7-Dimethyl-2,6-octadienal; (106-26-3)

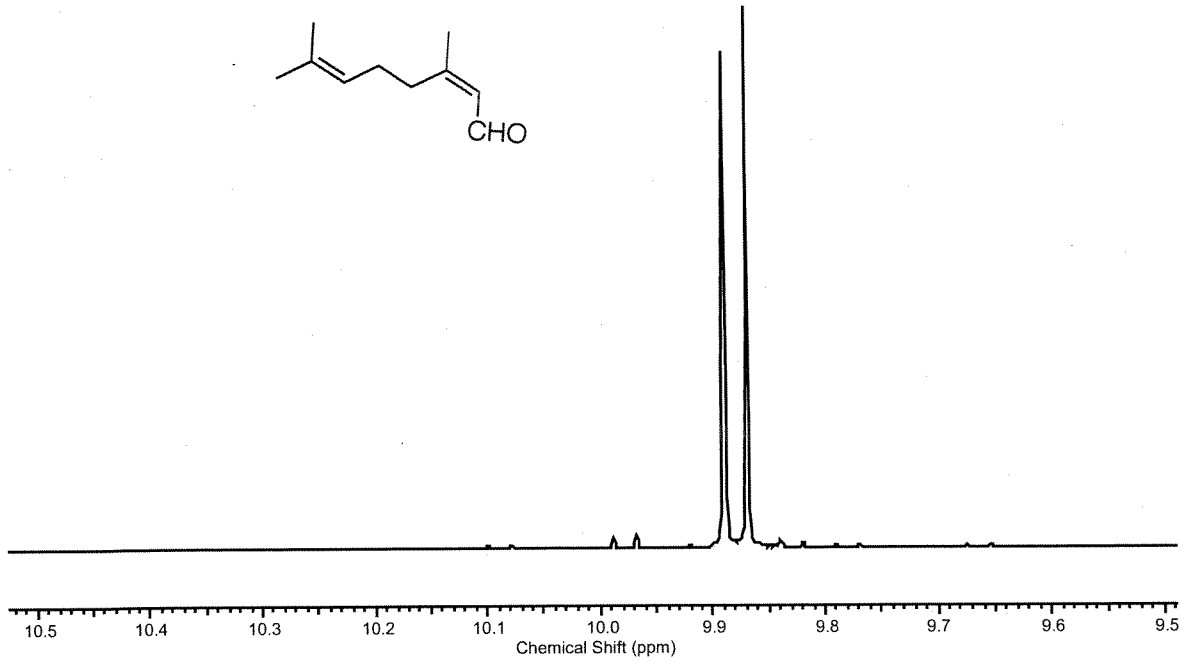
11 Aug 2005

Acquisition Time (sec)	2.3540	*Comment*	101226-144-2	*Date*	Aug 11 2005
File Name	\\giris30.pfizer.com\NMR\unityb\today\do-101226-144-2 h1				
Frequency (MHz)	399.95	*Nucleus*	1H	*Number of Transients*	16
Original Points Count	16000	*Points Count*	16384	*Pulse Sequence*	s2pul
Solvent	CHLOROFORM-D			*Sweep Width (Hz)*	6796.94
Temperature (degree C)	29.000				



11 Aug 2005

Acquisition Time (sec)	2.3540	*Comment*	101226-144-2	*Date*	Aug 11 2005
File Name	\\giris30.pfizer.com\NMR\unityb\today\do-101226-144-2_h1				
Frequency (MHz)	399.95	*Nucleus*	1H	*Number of Transients*	16
Original Points Count	16000	*Points Count*	16384	*Pulse Sequence*	s2pul
Solvent	CHLOROFORM-D			*Sweep Width (Hz)*	6796.94
Temperature (degree C)	29.000				



11 Aug 2005

Acquisition Time (sec)	0.6650	*Comment*	101226-144-2	*Date*	Aug 11 2005
File Name	\\giris30.pfizer.com\NMR\unityb\today\do-101226-144-2_c13				
Frequency (MHz)	100.58	*Nucleus*	13C	*Number of Transients*	256
Original Points Count	16384	*Points Count*	16384	*Pulse Sequence*	s2pul
Solvent	CHLOROFORM-D			*Sweep Width (Hz)*	24638.13
Temperature (degree C)	29.000