Organic Syntheses

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.

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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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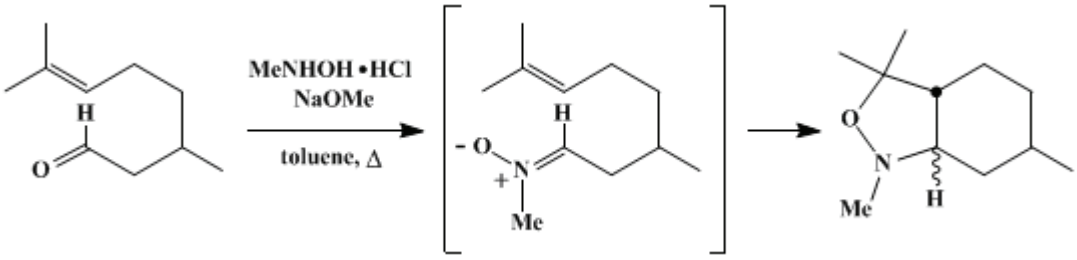
# NITRONES FOR INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS: HEXAHYDRO-1,3,3,6-TETRAMETHYL-2,1-BENZISOXAZOLINE

## [2,1-Benzisoxazole, 1,3,3*a*,4,5,6,7,7*a*-octahydro-1,3,3,6-tetramethyl-]




Submitted by Norman A. LeBel and Dorothy Hwang[1].
Checked by Christopher K. VanCantfort and Robert M. Coates.

## 1. Procedure

A 1-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a reflux condenser attached to a Dean-Stark water separator, and a 250-ml. dropping funnel. The flask is charged with 25.0 g. (0.16 mole) of 3,7-dimethyl-6-octenal (Note 1) and 500 ml. of toluene. The solution is heated to reflux with stirring, and a solution of *N*-methylhydroxylamine, methanol, and toluene is added (see below).

To a cooled and magnetically stirred solution of 23.4 g. (0.280 mole) of *N*-methylhydroxylamine hydrochloride (Note 2) and (Note 3) in 40 ml. of methanol is added 15.3 g. (0.282 mole) of sodium methoxide. The cooling bath is removed, and the mixture is stirred at room temperature for 15 minutes. The mixture is filtered rapidly through a 35-mm., coarse, sintered-glass funnel, and the filter cake is washed with 10 ml. of methanol. The filtrates are combined, refiltered, and mixed with 150 ml. of toluene.

The two-phase mixture containing *N*-methylhydroxylamine is added dropwise to the refluxing toluene solution of the aldehyde over 3 hours. During this time the distillate is collected and discarded in 25-ml. portions until the last such portion collected and discarded is clear (Note 4). Reflux and stirring are continued for an additional 3 hours, and then the clear reaction mixture is allowed to cool. The product is extracted with three 80-ml. portions of 10% hydrochloric acid. The extracts are combined, and the pH of the solution is adjusted to >12 by the slow addition of 30% aqueous potassium hydroxide. The basic mixture is extracted with two 120-ml. portions of pentane (Note 5), and the combined extracts are washed once with 100 ml. of water and dried over anhydrous potassium carbonate. The pentane is removed on a rotary evaporator, and the residue is distilled through a short Vigreux column under reduced pressure, yielding 19.1–19.6 g. (64–67%) (Note 6) of hexahydro-1,3,3,6-tetramethyl-2,1-benzisoxazoline, b.p. 90–92° (9 mm.) (Note 7).

## 2. Notes

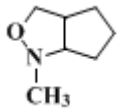
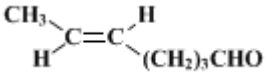
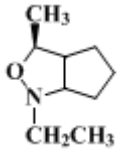
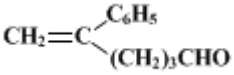
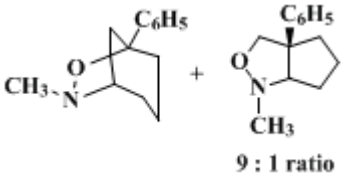
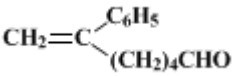
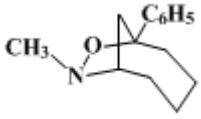
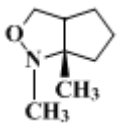
1. Matheson, Coleman and Bell technical grade 3,7-dimethyl-6-octenal (citronellal), b.p. 87–90° (10 mm.), is used after a simple distillation.
2. This quantity is a 0.72 molar excess. A molar excess of at least 0.5 is needed to maximize the yield.
3. *N*-Methylhydroxylamine hydrochloride, m.p. 83–84°, purchased from Aldrich Chemical Company, Inc., was used directly. Alternatively, the hydrochloride can be prepared by the reduction of nitromethane with zinc dust and ammonium chloride.[2]
4. Water and methanol are removed by this procedure, so that a higher reaction temperature can be

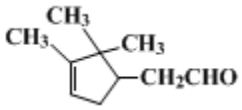
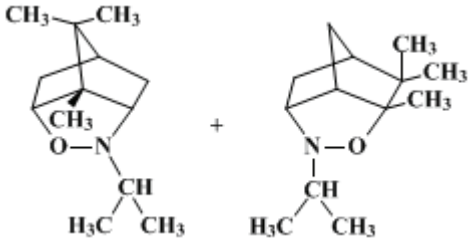
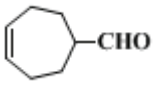
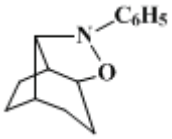
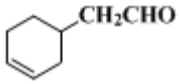
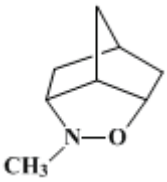
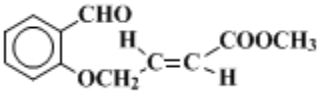
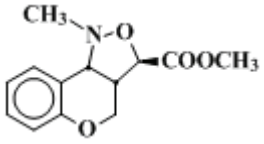
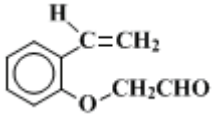
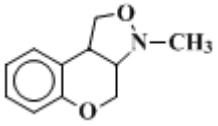
achieved.
5. One to four additional extractions improve the yield slightly.
6. The yield is lowered by the presence of 3,7-dimethyl-7-octenal in the technical grade 3,7-dimethyl-6-octenal (citronellal) used.
7. A GC analysis carried out by the submitters using a 1.85 m. × 0.32 cm. stainless-steel column packed with 10% Polyglycol E-20M on Chromosorb W at 150° indicated that the product is a mixture of *trans,trans* and *cis,trans* stereoisomers in a ratio of 89 : 11. The spectral properties of the product are: IR (thin film) $cm^{-1}$: 1462, 1387, 1348, 1287, 1277, 1193, 1179, 1136, 1124, 935, 915, 877, 810; $^1H$ NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.00 (d, *J* = 7, 3H, $CH_3$), 1.08 (s, 3H, $CH_3$), 1.28 (s, 3H, $CH_3$), 2.60 (s, 3H, $NCH_3$).

## 3. Discussion

This procedure is an adaptation[3] of the original method,[4] and avoids the isolation and purification of *N*-methylhydroxylamine. Nitrones undergo 1,3-dipolar cycloadditions with a wide variety of dipolarophiles (see recent review[5]). The intramolecular variation represents a useful synthetic approach, as carbocyclic or heterocyclic rings are generated together with the five-membered isoxazolidines.[6] The intermediate nitrone is usually not preformed (present example), although intermolecular cycloaddition is rarely a problem. *N*-alkyl-, *N*-alkenyl-, and *N*-arylhydroxylamines have been used with aldehydes and ketones to generate the nitrones *in situ*, and some typical examples are listed in Table I. Cyclic azomethine imine oxides are also important substrates for intramolecular cycloadditions.[6]

TABLE I
INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS OF NITRONES TO ALKENES

| Carbonyl Compound | Hydroxylamine | Product | Yield (%) |
|---|---|---|---|
| $CH_2$=CH$(CH_2)_3$CHO | $CH_3NHOH$ |  | 41[4] |
|  | $C_2H_5NHOH$ |  | 77[4] |
|  | $CH_3NHOH$ |  9 : 1 ratio | 87[15] |
|  | $CH_3NHOH$ |  | 78[15] |
|  | $CH_3NHOH$ |  | 80[7] |

| | | | |
|---|---|---|---|
|  | $(CH_3)_2CHNHOH$ |  | 70–80[8] |
|  | $C_6H_5NHOH$ |  | 88[9] |
|  | $CH_3NHOH$ |  | 55.4[10] |
|  | $CH_3NHOH$ |  | 80[11] |
|  | $CH_3NHOH$ |  | 10[12] |

Although isoxazolidines are less basic than the analogous amines, *N*-alkylisoxazolidines can form quaternary ammonium salts. Reductive cleavage of isoxazolidines and the methiodides can be effected with various reagents (zinc–acetic acid, hydrogen–palladium, lithium aluminum hydride), and the yields of 1,3-aminoalcohols are generally excellent.[4] Other reagents that result in modifications of the isoxazolidine ring include peroxyacids,[13] strong bases,[14] triplet photosensitizers,[14] and cyanogen bromide.[15]

## References and Notes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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Hexahydro-1,3,3,6-tetramethyl-2,1-benzisoxazoline

2,1-Benzisoxazole, 1,3,3a,4,5,6,7,7a-octahydro-1,3,3,6-tetramethyl-

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

zinc (7440-66-6)

palladium (7440-05-3)

Pentane (109-66-0)

hydroxylamine (7803-49-8)

Nitromethane (75-52-5)

Cyanogen bromide (506-68-3)

lithium aluminum hydride (16853-85-3)

3,7-dimethyl-6-octenal,
citronellal (106-23-0)

3,7-dimethyl-7-octenal

N-methylhydroxylamine (593-77-1)

N-methylhydroxylamine hydrochloride (4229-44-1)