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# Working with Hazardous Chemicals

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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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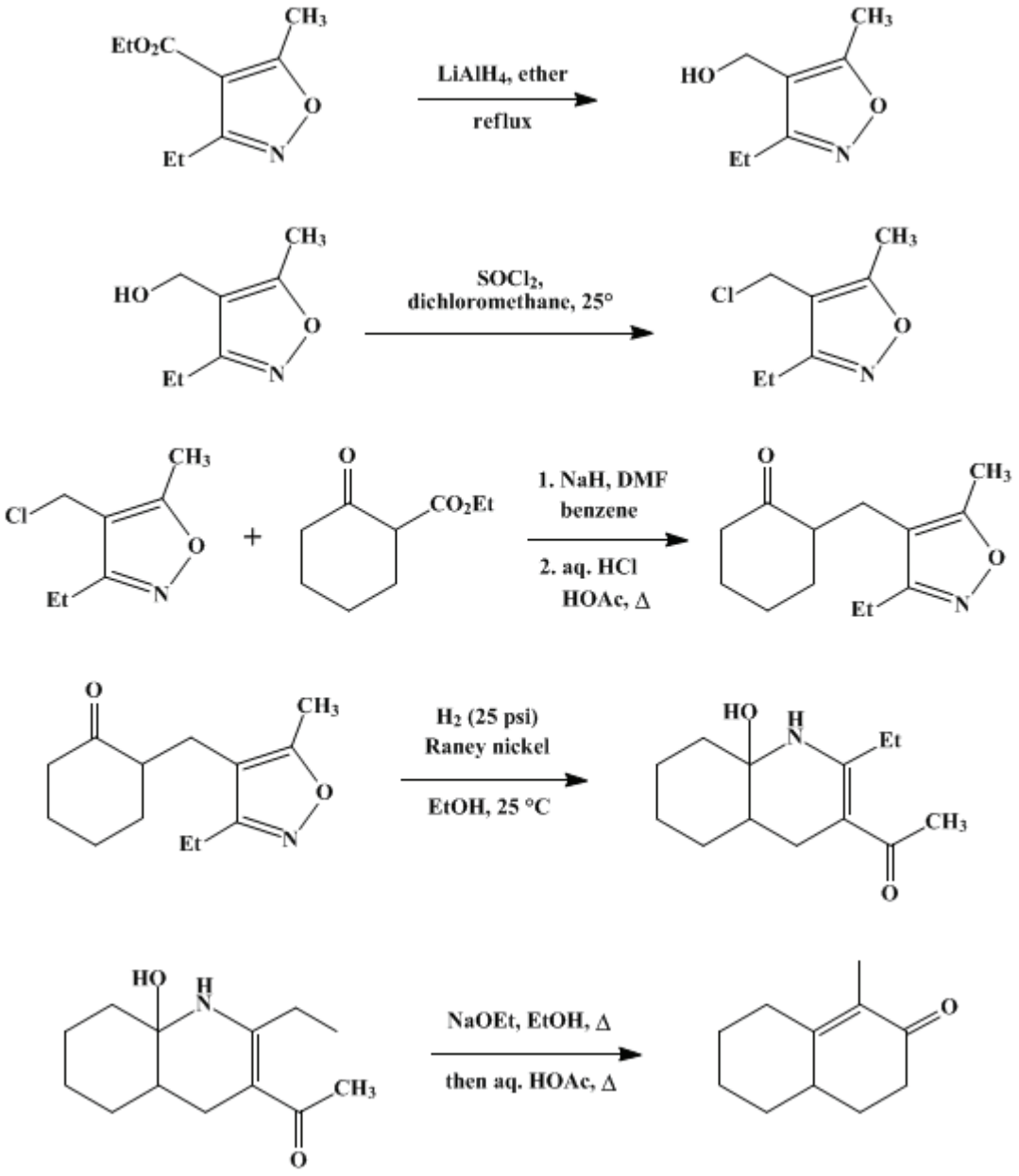
# ISOXAZOLE ANNELATION REACTION: 1-METHYL-4,4a,5,6,7,8-HEXAHYDRONAPHTHALEN-2(3*H*)-ONE

## [2(3*H*)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-1-methyl-]




Submitted by John E. McMurry[1]
Checked by U. P. Hochstrasser and G. Büchi.

## 1. Procedure

*Caution! Lithium aluminum hydride can react with explosive violence on contact with water or when overheated, and great care must be taken in its handling.*[1]

*Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.*

A. 3-*Ethyl*-4-*hydroxymethyl*-5-*methylisoxazole*. A slurry of lithium aluminum hydride (21.0 g., 0.553 mole) in anhydrous diethyl ether is prepared by cautiously adding the powdered reagent (Note 1) to 2.5 l. of freshly prepared anhydrous ether in a 5-l., three-necked flask fitted with a reflux condenser, a 500-ml. pressure-equalizing addition funnel, and a strong mechanical stirrer. The contents of the flask are then placed under a nitrogen atmosphere *via* a gas-inlet tube attached to the top of the condenser. Ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate (124 g., 0.678 mole) (Note 2), dissolved in 300 ml. of dry ether, is placed in the addition funnel and added dropwise over 4 hours to the lithium aluminum hydride slurry (Note 3). The reaction is refluxed gently for 4 hours, then placed in an ice bath. Quenching of excess reagent and hydrolysis of aluminate salts is effected by *cautious*, *slow* addition of 20 ml. of water, followed by 30 ml. of aqueous 10% sodium hydroxide and another 30 ml. of water (Note 4). The ether layer is filtered from granular aluminum salts, poured into a 2-l. separatory funnel, and washed with 250 ml. of saturated brine. The organic extract is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed with a rotary evaporator. The residual oil is distilled, yielding 76–82 g. (80–86%) of 3-ethyl-4-hydroxymethyl-5-methylisoxazole, b.p. 99–101° (0.15 mm.); $n_D^{23}$ 1.4835; IR: 3450, 1640 cm.$^{-1}$; $^1$H NMR ($CCl_4$): δ 1.2 (t, 3H, $CH_2CH_3$), 2.2 (s, 3H, C=C$CH_3$), 2.6 (q, 2H, $CH_2CH_3$), 4.2 (s, 2H, $CH_2O$).

B. 4-*Chloromethyl*-3-*ethyl*-5-*methylisoxazole*. *Caution! The following reaction should be carried out in a fume hood to avoid thionyl chloride vapors.*

3-Ethyl-4-hydroxymethyl-5-methylisoxazole (54 g., 0.38 mole) is dissolved in 70 ml. of dichloromethane and placed in a 500-ml., one-necked flask fitted with a 100-ml., pressure-equalizing addition funnel and a magnetic stirrer. The flask is placed in an ice bath, and its contents are stirred while a solution of 53 g. of thionyl chloride (32 ml., 0.45 mole) in 50 ml. of dichloromethane is added dropwise. Addition is complete in 1 hour, and the reaction is allowed to warm to room temperature and stirred for an additional hour. The solvent is removed with a rotary evaporator and the dark residual liquid is distilled, yielding 47–49 g. (78–81%) of 4-chloromethyl-3-ethyl-5-methylisoxazole, b.p. 77–78° (1.5 mm.); $n_D^{23}$ 1.4845; IR: 1620, 680 cm.$^{-1}$; $^1$H NMR ($CCl_4$): δ 1.3 (t, 3H, $CH_2CH_3$), 2.3 (s, 3H, C=C$CH_3$), 2.6 (q, 2H, $CH_2CH_3$), 4.3 (s, 2H, $CH_2Cl$).

C. 2-(3-*Ethyl*-5-*methyl*-4-*isoxazolylmethyl*)*cyclohexanone*. Sodium hydride (10.0 g. of a 60% slurry in mineral oil, 0.25 mole) is degreased in a flame-dried, 1-l., three-necked flask fitted with a 250-ml., pressure-equalizing addition funnel and a condenser through which a stream of nitrogen is blown. The sodium hydride is washed by adding 20 ml. of dry benzene, stirring magnetically, allowing it to settle, and drawing off the supernatant benzene wash with a syringe. The washing process is repeated four more times before 100 ml. of dry benzene is added, followed with 100 ml. of dry *N,N*-dimethylformamide (Note 5). The contents of the flask are covered with a nitrogen atmosphere and a solution of ethyl 2-cyclohexanonecarboxylate (41.0 g., 0.241 mole) (Note 6) in 100 ml. of 1:1 benzene–dimethylformamide is added slowly over 45 minutes, with cooling, keeping the reaction mixture near room temperature (Note 7). A solution of 4-chloromethyl-3-ethyl-5-methylisoxazole (32 g., 0.20 mole) in 100 ml. of 1:1 benzene–dimethylformamide is then added over 30 minutes, and the reaction is stirred for 2 days at room temperature. The reaction is diluted with 300 ml. of ether, poured into a 1-l. separatory funnel, washed three times with 100-ml. portions of water and once with brine, dried over anhydrous magnesium sulfate and filtered. The solvents are removed with a rotary evaporator, and the residual oil is dissolved in 150 ml. of glacial acetic acid and placed in a 500-ml., one-necked flask fitted with a magnetic stirrer and a reflux condenser. Hydrochloric acid (150 ml., 6 *N*) is added. The mixture is refluxed for 36 hours (Note 8), then concentrated with a rotary evaporator. The residue is taken up in 500 ml. of ether, poured into a 1-l. separatory funnel, and washed twice with 100-ml. portions of water, once with 5% aqueous sodium hydroxide, and once with brine. After drying over anhydrous magnesium sulfate and filtration, the organic extracts are concentrated with a rotary evaporator and distilled (Note 9), yielding 33–35 g. (75–80%) of 2-(3-ethyl-5-methyl-4-isoxazolylmethyl)cyclohexanone, b.p. 130°

(0.001 mm.); $n_D$ 1.4970; IR: 1710, 1630 cm.$^{-1}$; $^1$H NMR ($CCl_4$): δ 1.2 (t, 3H, $CH_2CH_3$). 1.5–2.2 (m, 11H, $5CH_2$ and C*H*), 2.3 (s, 3H, C=CC$H_3$), 2.5 (q. 2H, $CH_2CH_3$).

D. 1-*Methyl*-4,4a,5,6,7,8-*hexahydronaphthalen*-2(3H)-*one*. *Caution! Sodium ethoxide formation should be carried out in a hood since a large volume of hydrogen gas is evolved.*

2-(3-Ethyl-5-methyl-4-isoxazolylmethyl)cyclohexanone (27.6 g., 0.125 mole) is dissolved in 250 ml. of ethanol in a Parr hydrogenation bottle, and 20 g. of freshly prepared W-4 Raney nickel catalyst (Note 10) is added. Hydrogenation is started at an initial hydrogen pressure of 25 p.s.i. Cleavage of the isoxazole ring is complete after 6 hours, after which time the reaction is stopped and the solution is filtered free of catalyst (Note 11). The catalyst is washed with ether and absolute ethanol, and the combined organic filtrates are concentrated with a rotary evaporator (Note 12).

The viscous, residual liquid is dissolved in 25 ml. of absolute ethanol and a stream of nitrogen is bubbled through the solution for 15 minutes, removing dissolved oxygen (Note 13). A solution of sodium ethoxide is then prepared by cautiously dissolving freshly cut sodium (11.5 g., 0.500 mole) in 150 ml. of absolute ethanol, under a nitrogen atmosphere, in a 500-ml., three-necked flask fitted with a reflux condenser topped with a gas-inlet, a magnetic stirrer, and a rubber serum cap on one of the sidearms. When ethoxide formation is complete, the deoxygenated solution of the hydrogenated isoxazole is injected into the stirred reaction mixture through the rubber serum cap with a syringe. The solution is refluxed until the UV spectrum of a small aliquot withdrawn with a syringe through the serum cap shows the absence of absorption at 345 nm. (Note 14). This requires about 30 hours.

A solution of 15 ml. of glacial acetic acid and 30 ml. of water is deoxygenated as described above and slowly injected with a syringe into the reaction. Refluxing is continued for 6 hours, the flask is cooled, and its contents are poured into a 1-l. separatory funnel along with 200 ml. of water. The solution is extracted four times with 100-ml. portions of ether, and the combined ether extracts are washed successively with 100 ml. of 6 *N* hydrochloric acid, 100 ml. of water, and 100 ml. of brine. The organic extracts are dried over anhydrous magnesium sulfate, filtered, concentrated with a rotary evaporator, and distilled, yielding 13.2–13.8 g. (65–67%) of 1-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one, b.p. 85–90° (0.5 mm.); $n_D^{23}$ 1.5120; IR: 1670, 1605 cm.$^{-1}$; $^1$H NMR ($CCl_4$): δ 1.0–2.5 (m, 13H, $6CH_2$ and C*H*), 1.7 (s, 3H, C=CC$H_3$).

## 2. Notes

1. The reagents used in this procedure were obtained from the following sources: lithium aluminum hydride, Alfa Inorganic, Inc.; thionyl chloride, Matheson, Coleman and Bell; sodium hydride, Metal Hydrides, Inc. The nitrogen was prepurified.
2. See *Org. Synth.*, **Coll. Vol. 6**, 592 (1988).
3. The addition must be done cautiously and the reaction watched constantly to see that efficient stirring is maintained. When the addition is approximately half-complete, doughy lumps, which tend to form on top of the solution, impede the stirring.
4. This quenching procedure is mentioned in the literature.[2]
5. *N,N*-Dimethylformamide was dried and purified by distillation from anhydrous copper sulfate.
6. Ethyl cyclohexanonecarboxylate was purchased from Aldrich Chemical Company, Inc., and contains approximately 40% methyl ester. The amount used takes this fact into account.
7. *N,N*-Dimethylformamide begins to decompose if the temperature rises too much.
8. The submitter stated that 24 hours of refluxing was sufficient for complete decarboxylation; however, the checkers found that after 24 hours at reflux, approximately 30% of the ester remained. Analysis was performed by GC (6-ft. column, 10% silicon rubber, 210°).
9. The distillation is most conveniently done in a short-path distillation apparatus with a mercury diffusion pump.
10. The W-4 Raney nickel is prepared according to the literature.[3]
11. *Caution! Since the catalyst is highly pyrophoric when dry, do not dry it completely.*
12. The hydrogenated isoxazole is quite sensitive to air and heat and should be used as soon as possible to prevent decomposition.
13. Oxygen must be rigorously avoided, particularly in smaller scale reactions, to prevent oxidation of the dihydropyridine intermediate to the corresponding pyridine.

14. The absorption maximum at 345 nm. corresponds to an acetyldihydropyridine intermediate (see Discussion) and disappears when the acetyl group is cleaved by ethoxide. Thus, the reaction can be readily followed spectroscopically.

## 3. Discussion

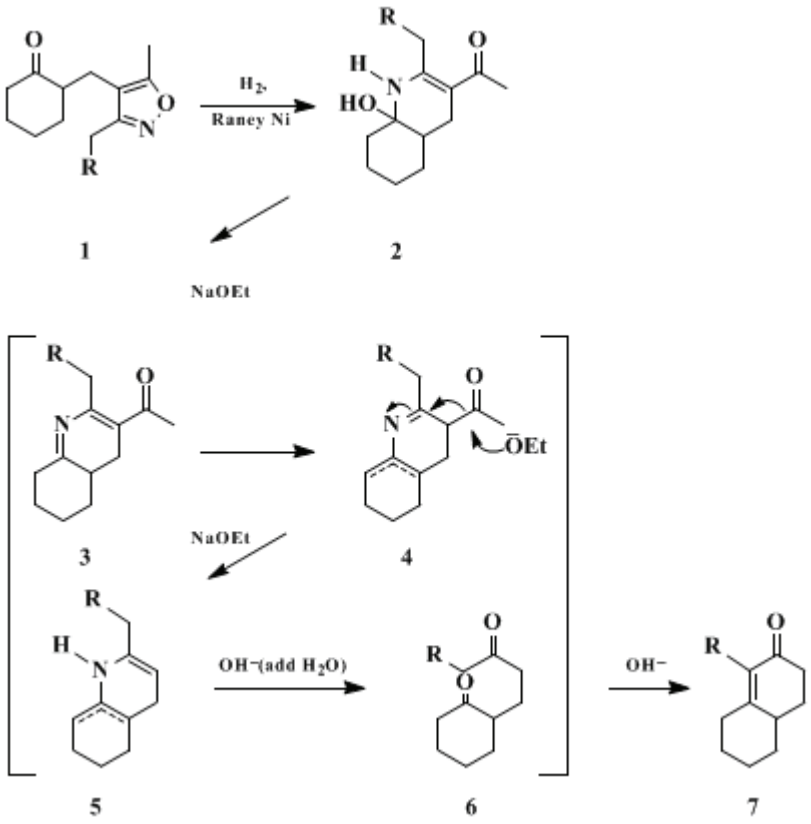
The isoxazole annelation reaction[4,5] is a general method for fusing a new cyclohexanone ring onto an existing system and complementary to the well-known Robinson annelation.[6] It has several major advantages:

1. The isoxazole ring serves as a "masked" or protected 3-oxobutyl side chain which can be positioned *alpha* to the existing ketone at an early stage in a complex synthesis. The isoxazole ring is stable to acids, bases, and hydride reducing agents[7] but can be cleanly and selectively cleaved by hydrogenolysis. Thus, at an appropriate time, the 3-oxobutyl side chain can be unmasked and annelation completed.

2. Although the present procedure attaches the isoxazole *via* alkylation of a β-keto ester, there are several different methods by which attachment could have been effected. Both alkylation of a cyclohexanone enamine[8] and direct alkylation of an enone anion followed by hydrogenation of the enone double bond have been used successfully.[4,5]

3. Since a wide range of 3-substituted-4-chloromethylisoxazoles can be easily prepared, the isoxazole annelation sequence allows one to construct a variety of substituted cyclohexenone systems.

The mechanism of the annelation sequence is of some interest and has been shown to proceed through the following path:[9]




The anhydrous, deoxygenated sodium ethoxide solution readily dehydrates carbinolamide **2** to the acyldihydropyridine **3**, but prevents hydrolysis or oxidation of **3**. Base-catalyzed double bond migrations can lead to **4**, the imine of a β-diketone, and the acetyl fragment can then be cleaved. Addition of water to the reaction causes hydrolysis of the cross-conjugated dienamine **5** to diketone **6**,

which then cyclizes.

The present procedure is illustrative of the general method which finds its utility largely in the construction of more complex polycyclic systems. The specific compound synthesized herein can be made more conveniently by standard Robinson annelation techniques.[10]

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

brine

W-4 Raney nickel

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

pyridine (110-86-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

ethoxide

ethyl 2-cyclohexanonecarboxylate,
Ethyl cyclohexanonecarboxylate (1655-07-8)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide,
dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

dihydropyridine

cyclohexenone (930-68-7)

isoxazole (288-14-2)

Ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate (53064-41-8)

3-Ethyl-4-hydroxymethyl-5-methylisoxazole (53064-42-9)

4-Chloromethyl-3-ethyl-5-methylisoxazole (40500-39-8)

2-(3-Ethyl-5-methyl-4-isoxazolylmethyl)cyclohexanone (53984-03-5)

acetyldihydropyridine

cyclohexanone enamine

carbinolamide (4312-87-2)

1-Methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one,
2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-1-methyl- (5164-37-4)