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of Reliable Methods  
for the Preparation  
of Organic Compounds

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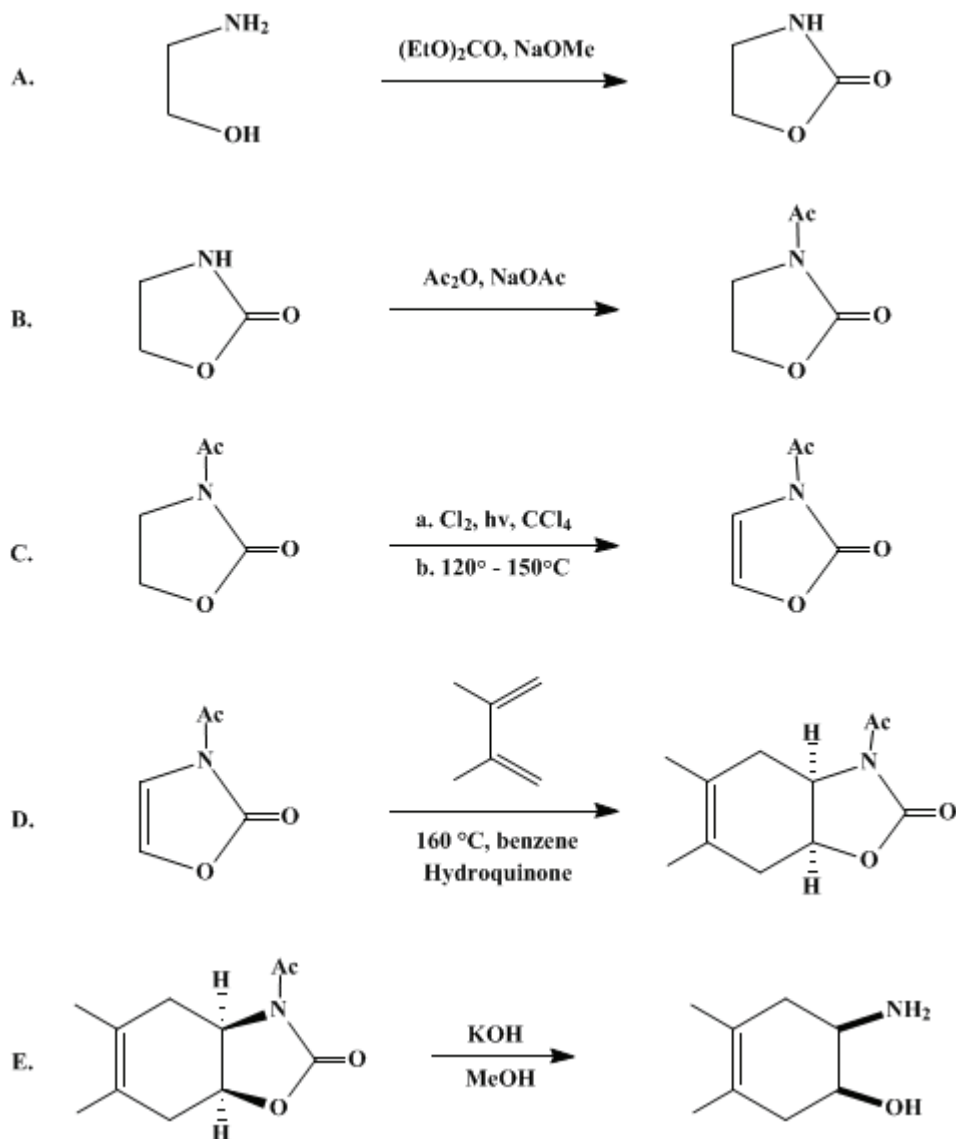
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## SYNTHESIS AND DIELS–ALDER REACTIONS OF 3-ACETYL-2-(3*H*)-OXAZOLONE: 6-AMINO-3,4-DIMETHYL-*cis*-3-CYCLOHEXEN-1-OL

[2(3*H*)-Oxazolone, 3-acetyl- and 3-cyclohexen-1-ol, 6-amino-3,4-dimethyl-, *cis*-]



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### 1. Procedure

A. *2-Oxazolidinone*. A 2-L, three-necked flask equipped with a thermometer, magnetic stirring bar, and a Vigreux column fitted with a distillation head is charged with 305 g (5.0 mol) of freshly distilled 2-aminoethanol, 730 g (6.2 mol) of diethyl carbonate, and 2.5 g (0.05 mol) of sodium methoxide (Note 1). The mixture is stirred and the flask is heated in an oil bath maintained at 125–130°C. Ethanol begins to distill off when the internal temperature reaches 95–100°C. After heating for about 8 hr, the internal temperature reaches 125°C and ethanol ceases to distill (Note 2). The reaction mixture is allowed to

cool to 60–70°C and is poured into 1 L of cold chloroform (Note 3). The resulting solution is chilled thoroughly in an ice–water bath and the precipitated product is recovered by filtration. The filtrate is concentrated to 250 mL and chilled to give a second crop. The combined crops are dried in a vacuum oven at 50°C to give 320–339 g (74–78%) of white crystals, mp 86–88°C [lit.<sup>2</sup> mp 87–89°C] (Note 4).

B. *3-Acetyl-2-oxazolidinone*. A 3-L, one-necked flask equipped with a reflux condenser and a magnetic stirring bar is charged with 326 g (3.75 mol) of 2-oxazolidinone, 94 g (1.15 mol) of anhydrous sodium acetate, and 1.6 L of acetic anhydride. The stirred solution is refluxed for 3 hr and the acetic anhydride is then removed by distillation at 15–20 mm. The residue is extracted with three 875-mL portions of boiling toluene (Note 5), and the hot toluene extractions are filtered, combined, and concentrated to a total volume of 675 mL. Diethyl ether (675 mL) is added with stirring to the toluene solution and the mixture is chilled in an ice–water bath. The precipitate is removed by filtration and washed with 250 mL of diethyl ether to give 328–403 g (68–83%) of colorless to very light tan crystals, mp 65–67°C [lit.<sup>2</sup> mp 69–70°C] (Note 6). A second crop of 63–24 g (13–5%), mp 65–68°C, is obtained by concentrating the filtrate to 275 mL and chilling it in an ice–water bath.

C. *3-Acetyl 4- and 5-chloro-2-oxazolidinone*. A 3-L, four-necked flask is equipped with a reflux condenser topped with a gas discharge tube, thermometer, fritted-glass inlet tube extending to the bottom of the flask, and a glass sleeve for accepting an ultraviolet (UV) lamp (Note 7). The reaction vessel is charged with 258 g (2.0 mol) of 3-acetyl-2-oxazolidinone, 2 L of carbon tetrachloride, and several boiling chips. The mixture is heated to gentle reflux, the light source is turned on, and 155 g (2.18 mol) of chlorine gas (Note 8) is introduced at such a rate that no chlorine escapes from the condenser (Note 9). After the addition is complete, heating is discontinued and nitrogen is bubbled through the reaction mixture to remove the dissolved hydrogen chloride. The solvent is then removed on a rotary evaporator to give a yellow oil, which consists of a mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinones<sup>3</sup> and is used in Step D without further purification.

D. *3-Acetyl-2(3H)-oxazolone*. The crude mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinone from Step C is placed in a 2-L, three-necked flask equipped with a thermometer, sealed mechanical stirrer, and gas discharge tube. The material is heated to 120°C with stirring, and the temperature is then slowly increased to 150°C and held there until the evolution of gas ceases (Note 10). The cooled, black reaction mixture is distilled at 20 mm. The fractions boiling up to 150°C are collected and redistilled through a 50-cm × 3-cm Vigreux column fitted with a variable take-off head. There is obtained 140–172 g (55–68%) of product, bp 108–112°C (24 mm), which solidifies, mp 35–37°C (Note 11).

E. *4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one*. A solution of 63.5 g (0.5 mol) of 3-acetyl-2(3H)-oxazolone, 27.5 g (0.33 mol) of 2,3-dimethylbutadiene (Note 12), and 2.0 g of hydroquinone in 125 mL of benzene is heated at 160°C under nitrogen in a 360-ml Hastelloy C shaker tube (Note 13). After 12 hr, the pressure vessel is cooled to room temperature, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated another 12 hr at 160°C. The vessel is again cooled, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated at 160°C for a final 12 hr. The resulting mixture is distilled to give 36.4–40.3 g (35–39%) of crude product, bp 115–130°C (0.5 mm), which solidifies (Note 14) and (Note 15). This material can be recrystallized by adding 36.4 g of melted product to 50 mL of boiling hexane, followed by cooling to give 27.6 g (26%) of crystals, mp 72–78°C (Note 16).

F. *6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol*. A solution of 26.1 g (0.125 mol) of 4-acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one and 42.0 g (0.75 mol) of potassium hydroxide in 200 mL of methanol and 100 mL of water is refluxed for 36 hr. The resulting mixture is exhaustively extracted with diethyl ether using a liquid–liquid continuous extraction apparatus. The ethereal extract is concentrated on a rotary evaporator and the residue is taken up in 150 mL of methylene chloride. The resulting solution is dried over anhydrous sodium sulfate, the drying agent is removed by filtration, and the filtrate is concentrated to dryness. The solid residue (16.5 g) is recrystallized from 100 mL of diethyl ether to give 11.2 g (64%) of colorless crystals, mp 63–65.5°C. A second crop of 2.3 g (13%) is obtained by concentrating the mother liquor to 50 mL and chilling in an ice–water bath (Note 17).

## 2. Notes

1. The checkers obtained 2-aminoethanol, diethyl carbonate, and anhydrous sodium methoxide from the

Aldrich Chemical Company.

2. About 625 mL (theoretical: 583 mL) of **ethanol** is collected. If the reaction is stopped before this volume is collected, the yield is reduced.

3. If the reaction mixture cools below 60°C, the product solidifies in the flask.

4. The product shows the following <sup>1</sup>H NMR spectrum (*d*<sub>6</sub>-DMSO) δ: 3.3–3.8 (m, 2 H), 4.2–4.6 (m, 2 H), 6.5–7.5 (br s, 1 H) and is analytically pure. Anal. calcd. for C<sub>3</sub>H<sub>5</sub>NO<sub>2</sub>: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.61; H, 5.70; N, 16.06. The submitters report that they obtained pure material, mp 89–90°C, after three recrystallizations from **chloroform**.

5. This is conveniently done by adding the **toluene** to the residue in the flask, heating to reflux in an oil bath, and then filtering the hot mixture.

6. This material shows the following <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) δ: 2.49 (s, 3 H), 3.8–4.7 (complex m, 4 H) and has acceptable analysis. Anal. calcd. for C<sub>5</sub>H<sub>7</sub>NO<sub>3</sub>: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.49; H, 5.40; N, 10.99. The submitters report that they obtained colorless, analytically pure material, mp 69–70°C, after three recrystallizations from **benzene**.

7. The submitters used a Philips HPK 125-W high-pressure **mercury** vapor lamp. The sleeve is 2-mm Pyrex glass with an NS45 ground joint. The lamp does not require cooling. The checkers obtained equally good results by shining a Westinghouse 250-W sun lamp on the reaction flask from a distance of 25 cm.

8. The **chlorine** gas is passed successively through three wash bottles. The center bottle is filled with concentrated **sulfuric acid** and the other two are left empty to serve as safety traps.

9. The photochlorination takes 4–6 hr. The **hydrogen chloride** evolved is absorbed in water.

10. Dehydrochlorination begins at about 120°C. The temperature is raised about 10°C/hr to 150°C to avoid vigorous gas evolution. The elimination of **hydrogen chloride** is complete after 5–6 hr.

11. The submitters report yields of 150–200 g, and that analytically pure material boils at 110°C (24 mm) and melts at 35–37°C after recrystallization from **diethyl ether**. The material obtained by the checkers showed a satisfactory analysis without further purification. Anal. calcd. for C<sub>5</sub>H<sub>5</sub>NO<sub>3</sub>: C, 47.25; H, 3.97; N, 11.02. Found: C, 46.81; H, 4.00; N, 11.21. The material shows the following <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) δ: 2.63 (s, 3 H), 6.90 (d, 1 H, *J* = 2.5), 7.30 (d, 1 H, *J* = 2.5); IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1880, 1735 (C=O).

12. The sample of **2,3-dimethylbutadiene** was obtained from the Aldrich Chemical Company.

13. The submitters employed a nickel autoclave and noted that product from Step D may contain a small amount of **hydrogen chloride** or chlorinated material that can adversely affect a stainless-steel pressure vessel. Hastelloy C is a high-nickel alloy.

14. The submitters obtained 48.0 g of product and 33.5 g of recovered starting material, bp 110°C (24 mm). The checkers found that the forerun collected at 108–112°C (24 mm) contained starting material, but it was highly contaminated with unidentified by-products.

15. The checkers obtained erratic results in this step, possibly because of surface effects or trace impurities in the pressure vessel. In two other runs, only 16.8–18.8 g of crude product were obtained. In one case, high-boiling oligomers were formed, but none of the desired product was produced. Impurities in the diene or dienophile did not appear to be the problem since runs that employed recrystallized **3-acetyl-2(3H)-oxazolone** and redistilled **2,3-dimethylbutadiene** also gave variable results.

16. The submitters report pure product with bp 135–137°C (1.2 mm) and mp 78–80°C after recrystallization from **chloroform**. The checkers found that recrystallization from **chloroform** gave very poor recovery of product with mp 75–78°C. Material with mp 72–78°C is pure by NMR, mass spectroscopy, and combustion analysis; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.70 (s, 6 H), 2.33 (m, 4 H), 2.45 (s, 3 H), 4.40 (d of t, 1 H, *J* = 9.0, 4.5), 4.83 (d of t, 1 H, *J* = 9.0, 4.5); infrared (IR) (KBr) cm<sup>-1</sup>: 1780, 1690. Mass spectrum *m/e* calculated: 209.1051. Found: 209.1030. Anal. calcd. for C<sub>11</sub>H<sub>15</sub>NO<sub>3</sub>: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.19; H, 7.10; N, 6.67.

17. The product shows the following <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) δ: 1.60 (s, 6 H), 2.13 (br m, 4 H), 2.30 (s, 3 H), 3.00 (m, 1 H), 3.80 (m, 1 H) and is analytically pure. Anal. calcd. for C<sub>8</sub>H<sub>15</sub>ON: C, 66.35; H, 10.71; N, 9.92. Found: C, 66.17, H, 10.48; N, 10.26.

### 3. Discussion

The dienophile, **3-acetyl-2(3H)-oxazolone**,<sup>4</sup> is an attractive intermediate for the synthesis of vicinal aminoalcohols with *cis* configurations. It reacts with 1,3-dienes, even under quite mild conditions, to form (4 + 2) cycloadducts.<sup>5, 6</sup> Its high reactivity with deactivated 1,3-dienes is noteworthy. This

property is present also in 2(3*H*)-oxazolone,<sup>4</sup> which can be obtained easily through solvolysis of 3-acetyl-2(3*H*)-oxazolone in methanol. 3-Acetyl-2(3*H*)-oxazolone, on UV irradiation in the presence of a sensitizer, combines easily with olefins to form (2 + 2) cycloadducts,<sup>7</sup> the hydrolysis of which leads to the class of *cis*-2-aminocyclobutanols.

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## References and Notes

1. Central Division for Research and Development, Main Scientific Laboratory of Bayer AG, D-4150, Krefeld-Uerdingen, West Germany.
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  5. Scholz, K.-H.; Heine, H.-G.; Hartmann, W. *Justus Liebigs Ann. Chem.* **1977**, 2027.
  6. Deyrup, J. A.; Gingrich, H. L. *Tetrahedron Lett.* **1977**, 3115.
  7. Scholz, K.-H.; Heine, H.-G.; Hartmann, W. *Tetrahedron Lett.* **1978**, 1467.
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## Appendix

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

3-acetyl 4- and 5-chloro-2-oxazolidinones

3-acetyl 4- and 5-chloro-2-oxazolidinone

[ethanol \(64-17-5\)](#)

[sulfuric acid \(7664-93-9\)](#)

[hydrogen chloride \(7647-01-0\)](#)

[Benzene \(71-43-2\)](#)

[methanol \(67-56-1\)](#)

[diethyl ether \(60-29-7\)](#)

[acetic anhydride \(108-24-7\)](#)

[sodium acetate \(127-09-3\)](#)

[chloroform \(67-66-3\)](#)

[hydroquinone \(123-31-9\)](#)

[sodium sulfate \(7757-82-6\)](#)

[carbon tetrachloride \(56-23-5\)](#)

[nitrogen \(7727-37-9\)](#)

mercury (7439-97-6)

sodium methoxide (124-41-4)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

methylene chloride (75-09-2)

2-aminoethanol (141-43-5)

diethyl carbonate (105-58-8)

2,3-Dimethylbutadiene (513-81-5)

hexane (110-54-3)

2-Oxazolidinone (497-25-6)

5-chloro-2-oxazolidinone

3-Acetyl-2-oxazolidinone (1432-43-5)

3-Acetyl-2(3H)-oxazolone,  
2(3H)-Oxazolone, 3-acetyl- (60759-49-1)

4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one (65948-43-8)

6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol,  
3-cyclohexen-1-ol, 6-amino-3,4-dimethyl-, cis- (65948-45-0)

2(3H)-oxazolone