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.

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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.
α,β-DEHYDROGENATION OF β-DICARBONYL COMPOUNDS BY SELENOXIDE ELIMINATION: 2-ACETYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 2-acetyl-]
stirred and cooled in an ice–salt bath as necessary to keep the temperature between 30 and 35° while the remainder of the hydrogen peroxide solution is added. When the oxidation is complete (Note 9), the ice–salt bath is removed, and vigorous stirring is continued for 15 minutes at room temperature and 15 minutes at 0°. The chilled suspension of benzeneseleninic acid is filtered, and the filter cake is washed with 50 ml. of dichloromethane (Note 10). The dichloromethane layer from the filtrate is washed with 50 ml. of aqueous 7% sodium hydrogen carbonate, dried by filtration through a cone of anhydrous sodium sulfate, and evaporated, providing 12.8–13.7 g. of crude product (Note 11). Distillation in carefully washed glassware (Note 12) at 0.1 mm. using a Kügelrohr apparatus (Note 13) with an oven temperature of 50–55° gives 11.0–11.9 g. (79–85%) of 2-acetyl-2-cyclohexen-1-one (Note 14).

2. Notes

1. A 57% dispersion of sodium hydride in mineral oil was purchased from Alfa Division, Ventron Corporation. A 5.90-g. portion of the dispersion was placed in the reaction vessel and washed free of mineral oil with three 50-ml. portions of pentane by decanting the supernatant pentane after each washing. The pentane that remains in the flask is evaporated as the assembled apparatus is purged with nitrogen prior to adding the tetrahydrofuran.

2. Tetrahydrofuran was purified by the submitters by distillation from the sodium ketyl of benzophenone.

3. 2-Acetylcyclohexanone was used as supplied by Aldrich Chemical Company, Inc.

4. Benzeneselenenyl chloride was prepared by the procedure in Org. Synth., Coll. Vol. 6, 533 (1988). A freshly prepared solution of 24.8 g. (0.105 mole) of benzeneselenenyl bromide in 25 ml. of tetrahydrofuran may also be used.

5. The crude selenide is contaminated by volatile impurities including some 2-acetylcyclohexanone which may be removed by sublimation at 50–60° to a cold finger cooled with dry ice, or by recrystallization from ether–pentane. The purified product melts at 72–73°; IR (CCl4) cm⁻¹: 1693 strong, 1579 weak; ¹H NMR (CCl4) δ (multiplicity, number of protons, assignment): 1.3–2.3 (m, 7H, ring protons), 2.30 (s, 3H, C₆H₃), 2.5–2.8 (m, 1H, CH₆H₅C=O), 7.28 (m, 5H, C₆H₅Se). The product was analyzed by the submitters. Analysis calculated for C₁₄H₁₆O₂Se: C, 56.96; H, 5.46. Found: C, 57.12; H, 5.48.

6. Dichloromethane was used without purification.

7. A 30% solution of hydrogen peroxide in water was purchased from Mallinckrodt Chemical Works. The reaction requires 2 molar equivalents of hydrogen peroxide, the first to oxidize the selenide to the selenoxide and the second to oxidize the elimination product, benzeneselenenic acid, to benzeneselenenic acid. The submitters recommend that the hydrogen peroxide solution be taken from a recently opened bottle, or titrated to verify its concentration.

8. The oxidation is autocatalytic, being catalyzed by the product, benzeneselenenic acid. If the temperature drops significantly below 30°, the addition of hydrogen peroxide should be stopped, and the ice–salt bath should be removed to maintain the rate of oxidation and avoid an accumulation of hydrogen peroxide in the flask.

9. The yellow dichloromethane solution turns colorless, and a precipitate of benzeneselenenic acid appears.

10. The benzeneselenenic acid weighs 14.4–16 g. (73–82%) and melts at 123–124°. It may be reconverted to diphenyl diselenide by reduction with sodium thiosulfate or sodium bisulfite.

11. The enol content of the product at this point is less than 2%. If the unenolized enedione is desired, the following distillation should be omitted and the product used without purification to avoid further isomerization.

12. The glassware was cleaned in a sodium dichromate–sulfuric acid bath, washed with aqueous 10% ammonium hydroxide, and rinsed with water. The extent of enolization apparently depends on the care taken in washing the glassware and conducting the distillation.


14. The product is contaminated by 5–15% of 2-acetylcyclohexanone, which was present in the crude selenide. This impurity may be avoided by purifying the selenide as described in (Note 5). The enol content of the product obtained by the submitters varied from 5 to 50%. At equilibrium the enol content is 84%. The spectral properties of the enedione are as follows: IR (CCl4) cm⁻¹: 1694 strong, 1602 weak; ¹H NMR (CCl4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.9–2.2
(m, 2H, CH₂CH₂), 2.35 (s, 3H, CH₃), 2.3–2.7 (m, 4H, CH₂CH₂CH₃), 7.56 (t, J = 4.3, H, CH₂CH=CH). The enol form of the product exhibits the following ¹H NMR (CCl₄), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 2.07 (s, 3H, CH₃), 2.1–2.7 (m, 4H, CH₂CH₂CH₂), 5.55 (d of t, J = 4.5 and 10, 1H, CH₂CH=CH), 6.19 (d of t, J = 1.5 and 10, 1H, CH₂CH=CH), 15.8 (s, 1H, OH).

3. Discussion

The procedure described here serves to illustrate a new, general method for effecting the α,β-dehydrogenation of ketones,2,5,6,7,8,9 α,β-aldehydes,9 esters,2,5,6,7,8 lactones,9,10 nitriles,11 sulfones, and related compounds.2,12 The individual steps in the process are formation of an α-carbanion or enol derivative, phenylselenenylation with diphenyl diselenide or benzene selenenyl halides, oxidation of the resulting α-phenylseleno compound to the selenoxide, and thermal syn-elimination of benzeneselenenic acid. The advantages of this method include (a) the ease of introducing the α-phenylseleno group; (b) the rapid stoichiometric oxidation of the selenide with aqueous hydrogen peroxide at 25–35°, sodium metaperiodate in aqueous media, or ozone in dichloromethane at –78°; and (c) the fact that the elimination occurs at about room temperature under essentially neutral conditions.

The mild character of the reaction conditions is exemplified effectively here by the preparation of 2-acetyl-2-cyclohexen-1-one from 2-acetylcytohexanone.2 The crude product is isolated without the less stable enedione form which is partially converted to the more stable enol form, 2-acetyl-1,3-cyclohexadiene-1-ol,13,14,15 during distillation at 45–55°. A series of α,β-unsaturated β-keto esters, β-diketones, and a β-keto sulfoxide have also been prepared in the unenolized form by this procedure (Table I).2,5,6,7 In the case of the highly sensitive ethyl 5-oxo-1-cyclopentene-1-carboxylate, the hydrogen carbonate extraction must be omitted to avoid base-catalyzed decomposition during isolation.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexane-1-one</td>
<td>81ᵇ</td>
<td>2-Acetyl-1,3-cyclohexadiene-1-ol</td>
<td>74</td>
</tr>
<tr>
<td>2-Acetyl-2-cyclohexene-1-one</td>
<td>89</td>
<td>2-Acetyl-2-cyclohexene-2-one</td>
<td>89</td>
</tr>
<tr>
<td>2-Acetyl-2-cyclohexene-1,3-dione</td>
<td>84</td>
<td>5-oxo-1-cyclopentene-1-carboxylate</td>
<td>55</td>
</tr>
</tbody>
</table>

ᵃ Overall yield from β-keto ester, β-diketone, or β-keto sulfoxide. The scale was 0.01–0.005 mole.
ᵇ The starting β-keto ester and the product were 2:1 mixtures of ethyl and methyl esters.

The enolized form of 2-acetyl-2-cyclohexen-1-one has been synthesized in low yield by dehydrochlorination of 2-acetyl-2-chlorocyclohexanone in collidine at 180°13,14 and by elimination of
acetamide from \(N\)-(2-acetyl-3-oxo-1-cyclohexyl)acetamide at 120–140\(^\circ\).\(^\text{15}\) The preparation of other \(\alpha,\beta\)-unsaturated \(\beta\)-dicarbonyl compounds has been attempted with varying degrees of success. The dehydrogenation of 2-hydroxymethylene-3-keto steroids to 2-formyl-\(\Delta^1\)-3-keto compounds with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone has been reported.\(^\text{16}\) Ethyl 5-oxo-1-cyclopentene-1-carboxylate has been prepared by selenium dioxide oxidation of the parent \(\beta\)-keto ester.\(^\text{17}\) \(\alpha\)-Acetoxylation of 3-methyl- and 3-isopropyl-2,4-pentanedione followed by acetate pyrolysis provided the \(\alpha,\beta\)-unsaturated \(\beta\)-diketones.\(^\text{18}\) Chlorination and dehydrochlorination of 2-acetylcycloheptanone gave an enolic tautomer of 2-acetyl-2-cyclohepten-1-one.\(^\text{14}\) Numerous failures in attempts to synthesize these and other \(\alpha,\beta\)-unsaturated \(\beta\)-dicarbonyl compounds by halogenation and dehydrohalogenation have been recorded as a consequence of competing Favorskii rearrangement, migration of halogen to the \(\alpha\)'-position, and decomposition of the products from a combination of the high temperatures and basic conditions employed.\(^\text{13,14,16,17,18,19}\) A number of \(\alpha,\beta\)-unsaturated \(\beta\)-keto esters and \(\beta\)-diketones have been prepared by intermolecular aldol condensations under Knoevenagel conditions,\(^\text{20}\) aldol cyclization,\(^\text{19,21}\) and Robinson annelation.\(^\text{22}\) All these procedures lead to equilibrium mixtures of keto and enol forms.

References and Notes

1. Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706.

Appendix

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

sodium ketyl
3-methyl- and 3-isopropyl-2,4-pentanedione

**Acetamide** (60-35-5)

**ether** (60-29-7)

**hydrogen** (1333-74-0)

**sodium hydrogen carbonate** (144-55-8)

**sodium chloride** (7647-14-5)

**sodium sulfate** (7757-82-6)

**sodium thiosulfate** (7772-98-7)

**nitrogen** (7727-37-9)

**sodium bisulfite** (7631-90-5)

**selenium dioxide** (7446-08-4)

**Benzophenone** (119-61-9)

**hydrogen peroxide** (7722-84-1)

**ammonium hydroxide** (1336-21-6)

**Pentane** (109-66-0)

**dichloromethane** (75-09-2)

**ozone** (10028-15-6)

**selenium**

**Tetrahydrofuran** (109-99-9)

**sodium hydride** (7646-69-7)

**hydrogen carbonate** (463-79-6)

**Diphenyl diselenide** (1666-13-3)

**collidine**

**2,3-dichloro-5,6-dicyano-1,4-benzoquinone**

**sodium metaperiodate** (7790-28-5)

**sulfoxide**
2-acetylhexan-1-one, 2-acetyl-2-cyclohexen-1-one, 2-Cyclohexen-1-one, 2-acetyl- (52784-38-0)

diethyl ether-pentane

2-acetyl-2-phenylselenocyclohexanone

Benzeneseleninic acid (6996-92-5)

Benzeneselenenyl chloride (5707-04-0)

benzeneselenenyl bromide (34837-55-3)

2-acetyl-1,3-cyclohexadien-1-ol

ethyl 5-oxo-1-cyclopentene-1-carboxylate

2-acetyl-2-chlorocyclohexanone

2-acetylcycloheptanone

2-acetyl-2-cyclohepten-1-one

N-(2-acetyl-3-oxo-1-cyclohexyl)acetamide

lead tetraacetate (546-67-8)