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.

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.

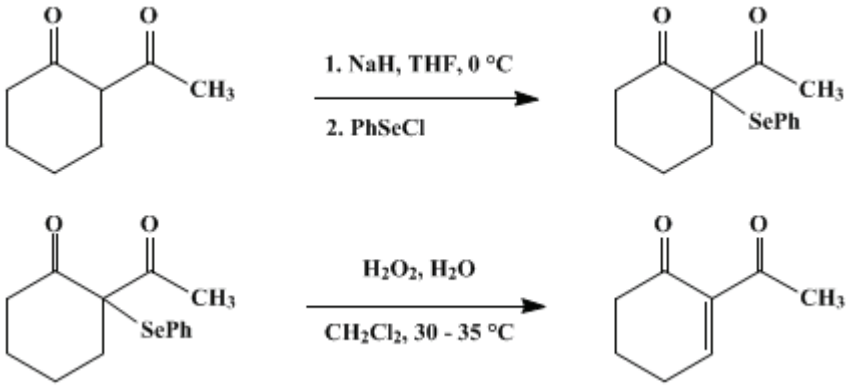
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.059.0058

Organic Syntheses, Coll. Vol. 6, p.23 (1988); Vol. 59, p.58 (1979).

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

[2-Cyclohexen-1-one, 2-acetyl-]



Submitted by James M. Renga and Hans J. Reich[1].
Checked by Albert W. M. Lee and Robert V. Stevens.

1. Procedure

Caution! Most selenium compounds are toxic; consequently care should be exercised in handling them. The hydrogen peroxide oxidation of selenides is highly exothermic, acid-catalyzed, and autocatalytic. The procedure given for adding the hydrogen peroxide solution should be carefully followed.

A. 2-*Acetyl*-2-*phenylselenocyclohexanone*. A 500-ml., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a combined inlet-outlet assembly connected to a nitrogen source and a bubbler. The flask is charged with 3.36 g. (0.140 mole) of sodium hydride (Note 1), the apparatus is flushed with nitrogen, and 100 ml. of tetrahydrofuran (Note 2) is added. The suspension is stirred and cooled in an ice bath under a static nitrogen atmosphere as a solution of 14.02 g. (0.100 mole) of 2-acetylcyclohexanone (Note 3) in 15 ml. of tetrahydrofuran is added over a 15-minute period. The formation of the sodium enolate is complete when hydrogen evolution ceases and a thick suspension has developed. Stirring and cooling are continued for 20 minutes, after which a solution of 20.1 g. (0.105 mole) of benzeneselenenyl chloride (Note 4) in 20 ml. of tetrahydrofuran is rapidly added. The contents of the flask are stirred at 0° for 15 minutes and poured into a beaker containing a magnetically stirred mixture of 200 ml. of 1:1 (v/v) diethyl ether-pentane, 50 ml. of aqueous 7% sodium hydrogen carbonate, and 50 g. of ice. The layers are separated, and the aqueous layer is extracted with 50 ml. of 1:1 (v/v) ether–pentane. The combined organic extracts are washed with 50 ml. of saturated aqueous sodium chloride and dried by filtration through a cone of anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure gives 29.2–30 g. of crude, solid 2-acetyl-2-phenylselenocyclohexanone which is used in Part B without purification (Note 5).

B. 2-*Acetyl*-2-*cyclohexen*-1-*one*. A 500-ml., three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, a reflux condenser, a thermometer, and a magnetic stirring bar is charged with a solution of 29.2–30 g. (*ca.* 0.1 mole) of crude 2-acetyl-2-phenylselenocyclohexanone in 100 ml. of dichloromethane (Note 6). The solution is stirred at room temperature, and a 2–3 ml. portion from a solution of 23.8 g. of 30% hydrogen peroxide (7.14 g., 0.21 mole) (Note 7) in 20 ml. of water is added to initiate the oxidation (Caution! (Note 8)). After the exothermic reaction begins, the mixture is

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[2] 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 (CCl_4) cm^{-1}: 1693 strong, 1579 weak; ^1H NMR (CCl_4) δ (multiplicity, number of protons, assignment): 1.3–2.3 (m, 7H, ring protons), 2.30 (s, 3H, CH_3), 2.5–2.8 (m, 1H, $CH_AH_BC{=}O$), 7.28 (m, 5H, C_6H_5Se). The product was analyzed by the submitters. Analysis calculated for $C_{14}H_{16}O_2Se$: 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 benzeneseleninic 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, benzeneseleninic acid.[3] 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 benzeneseleninic acid appears.
10. The benzeneseleninic 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[2] or sodium bisulfite.[4]
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.
13. Kügelrohr distillation ovens manufactured by Büchi Glasapparatfabrik are available from Brinckmann Instruments, Inc., Westbury, New York.
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 (CCl_4) $cm.^{-1}$: 1694 strong, 1602 weak; ^1H NMR (CCl_4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.9–2.2

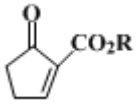
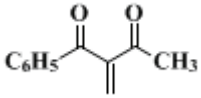
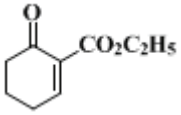
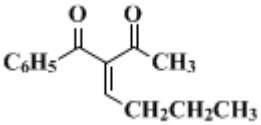
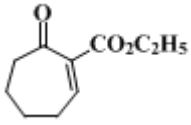
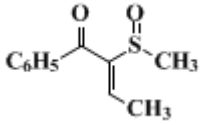
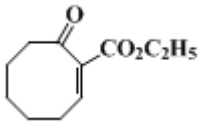
(m, 2H, $CH_2CH_2CH_2$), 2.35 (s, 3H, CH_3), 2.3–2.7 (m, 4H, $CH_2CH_2CH_2$), 7.56 (t, J = 4.3, H, CH_2CH=C). The enol form of the product exhibits the following ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 2.07 (s, 3H, CH_3), 2.1–2.7 (m, 4H, CH_2CH_2), 5.55 (d of t, J = 4.5 and 10, 1H, CH_2CH=CH), 6.19 (d of t, J = 1.5 and 10, 1H, CH_2CH=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] aldehydes,[9] esters,[2,5,6,7,9] 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-acetylcyclohexanone.[2] The crude product is initially isolated entirely in the less stable enedione form which is partially converted to the more stable enol form, 2-acetyl-1,3-cyclohexadien-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 I
α,β-UNSATURATED β-KETO ESTERS, β-DIKETONES AND A β-KETO SULFOXIDE PREPARED BY SELENOXIDE ELIMINATION

α,β-Unsaturated Product	Yield (%)[a]	α,β-UnsaturatedProduct	Yield (%)[a]
	81[b]		74
	89		89
	84		55
	89		

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°.[15] The preparation of other α,β-unsaturated β-dicarbonyl compounds has been attempted with varying degrees of success. The dehydrogenation of 2-hydroxymethylene-3-keto steroids to 2-formyl-Δ^1-3-keto compounds with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone has been reported.[16] Ethyl 5-oxo-1-cyclopentene-1-carboxylate has been prepared by selenium dioxide oxidation of the parent β-keto ester.[17] α-Acetoxylation of 3-methyl- and 3-isopropyl-2,4-pentanedione with lead tetraacetate followed by acetate pyrolysis provided the α,β-unsaturated β-diketones.[18] Chlorination and dehydrochlorination of 2-acetylcycloheptanone gave an enolic tautomer of 2-acetyl-2-cyclohepten-1-one.[14] Numerous failures in attempts to synthesize these and other α,β-unsaturated β-dicarbonyl compounds by halogenation and dehydrohalogenation have been recorded as a consequence of competing Favorskii rearrangement, migration of halogen to the α'-position, and decomposition of the products from a combination of the high temperatures and basic conditions employed.[13,14,16,17,18,19] A number of α,β-unsaturated β-keto esters and β-diketones have been prepared by intermolecular aldol condensations under Knoevenagel conditions,[20] aldol cyclization,[19,21] and Robinson annelation.[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.
2. H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
3. H. J. Reich, F. Chow, and S. L. Peake, *Synthesis*, 299 (1978).
4. K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974).
5. H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973);
6. H. J. Reich, J. M. Renga, and I. L. Reich, *J. Org. Chem.*, **39**, 2133 (1974);
7. H. J. Reich and J. M. Renga, *J. Org. Chem.*, **40**, 3313 (1975).
8. D. L. J. Clive, *J. Chem. Soc. Chem. Commun.*, 695 (1973).
9. K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).
10. P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974).
11. D. N. Brattesani and C. H. Heathcock, *Tetrahedron Lett.*, 2279 (1974).
12. For recent reviews, see H. J. Reich, *Acc. Chem. Res.*, **12**, 22 (1979); H. J. Reich, "Organoselenium Oxidations," in W. Trahanovsky, Ed., "Oxidation in Organic Chemistry," Part C, Academic Press, New York, 1978, pp. 1–130; D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978).
13. M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957);
14. C. W. T. Hussey and A. R. Pinder, *J. Chem. Soc.*, 3525 (1961).
15. A. A. Akhrem, A. M. Moiseenkov, and F. A. Lakhvich, *Izv. Akad. Nauk SSSR*, 407 (1972); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 355 (1972).
16. J. A. Edwards, M. C. Calzada, L. C. Ibanez, M. E. Cabezas Rivera, R. Urquiza, L. Cardona, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **29**, 3481 (1964).
17. J. N. Marx, J. H. Cox, and L. R. Norman, *J. Org. Chem.*, **37**, 4489 (1972).
18. D. Gorenstein and F. H. Westheimer, *J. Am. Chem. Soc.*, **92**, 634 (1970); C. W. T. Hussey and A. R. Pinder, *J. Chem. Soc.*, 1517 (1962).
19. J. A. Brenner, *J. Org. Chem.*, **26**, 22 (1962).
20. G. B. Payne, *J. Org. Chem.*, **24**, 1830 (1959); F. Tiemann and P. Krüger, *Ber. Dtsch. Chem. Ges.*, **28**, 2121 (1895).
21. S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1974).
22. G. Stork and R. N. Guthikonda, *J. Am. Chem. Soc.*, **94**, 5109 (1972).

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-acetylcyclohexanone (874-23-7)

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)