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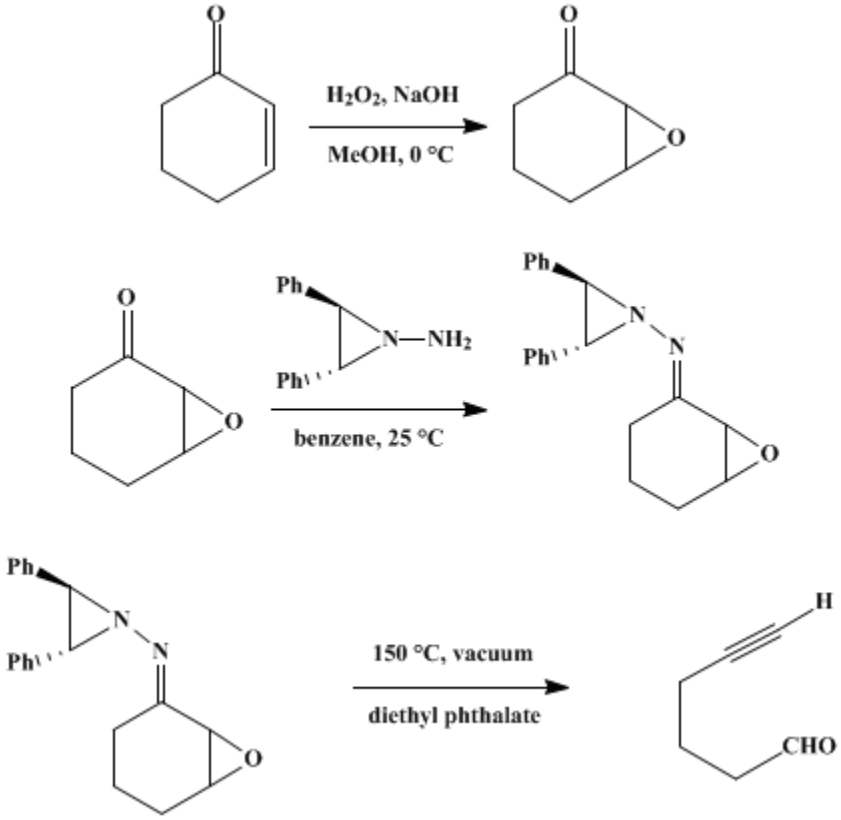
FRAGMENTATION OF α,β-EPOXYKETONES TO ACETYLENIC ALDEHYDES AND KETONES: PREPARATION OF 2,3-EPOXYCYCLOHEXANONE AND ITS FRAGMENTATION TO 5-HEXYNAL

[5-Hexynal]



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1. Procedure

A. 2,3-*Epoxycyclohexanone*. A 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirring bar and a thermometer is charged with a solution of 9.60 g. (0.100 mole) of 2-cyclohexen-1-one (Note 1) in 100 ml. of methanol. After the solution is cooled to 1–3° in an ice bath, 34 g. (30 ml., 0.30 mole) of 30% aqueous hydrogen peroxide (Note 2) is added. The mixture is stirred vigorously and kept well cooled in the ice bath, and 0.15 ml. (0.75 mmole) of 20% aqueous sodium hydroxide is added in one portion. The temperature of the reaction mixture rises to approximately 30° within a few minutes then falls again to 3–5°. Fifteen minutes after addition of the sodium hydroxide solution, the cold reaction mixture is poured into a 1-l. separatory funnel containing 150 g. of ice and 200 ml. of saturated aqueous sodium chloride. The resulting suspension is extracted with 200 ml. of dichloromethane. After two further extractions of the aqueous layer with 150-ml. portions of dichloromethane, the combined organic extracts are dried over anhydrous magnesium sulfate, and the solvent is removed by distillation through a 30-cm. Vigreux column (Note 3). Distillation of the residue through a 15-cm. Vigreux column under reduced pressure affords a forerun fraction of approximately 0.7 g., b.p. 60–75° (11 mm.) (Note 4), then 8.4–8.6 g. (75–77% of pure 2,3-epoxycyclohexanone (Note 5) and (Note 6), b.p. 75–77° (11 mm.), n_D^{20} 1.4748, d_4^{20} 1.129.

B. 5-*Hexynal*. To a solution of 5.60 g. (0.0500 mole) of 2,3-epoxycyclohexanone in 120 ml. of benzene in a 500-ml., round-bottomed flask is added 10.82 g. (0.5152 mole) of *trans*-1-amino-2,3-diphenylaziridine [*Org. Synth.*, **Coll. Vol. 6**, 56 (1988)]. Initially, after brief swirling at room temperature, the reaction mixture is a colorless, homogeneous solution; however it rapidly turns yellow and cloudy due to separation of water. After 2 hours the benzene and water are removed as an azeotrope on a rotary evaporator with the bath maintained at approximately 30°. The resulting crude mixture of diastereomeric hydrazones weighs 15.4 g. (Note 7) and is subjected directly to fragmentation (Note 8).

The fragmentation is conveniently performed in a 100-ml., wide-necked (Note 9), round-bottomed flask with a side arm. The side arm is equipped with a capillary fitted with a balloon filled with argon or nitrogen. The capillary should be set so that it does not dip into the reaction mixture. The reaction flask is equipped with a magnetic stirring bar and fitted with a short assembly for distillation under reduced pressure. A dropping funnel extends through the stillhead to a level about that of the neck of the flask, and the receiver is cooled in an ice bath. A trap is positioned between the receiver and the vacuum source and cooled in a 2-propanol–dry ice mixture. The reaction flask is immersed in an oil bath at 150–155°, and the apparatus is evacuated to a pressure of 11 mm. The crude hydrazone mixture is dissolved in 20 ml. of diethyl phthalate (Note 10) and carefully added in small portions, from the funnel, into the heated flask, with the stirrer in operation. There is a rapid evolution of nitrogen, and 5-hexynal begins to distil. Addition of the entire hydrazone solution requires approximately 2 hours, after which the funnel is washed with 5 ml. of diethyl phthalate, and the temperature of the reaction flask is raised to 160–165°. The reaction is complete when there is no further evolution of nitrogen. The last traces of product can be driven into the receiver by warming the stillhead with a heat gun.

The contents of the receiver and trap are combined with the aid of a few drops of dichloromethane and distilled through a 15-cm. Vigreux column under reduced pressure. After only a few drops of forerun, 2.87–3.17 g. (60–66%) of 5-hexynal, b.p. 61–62° (30 mm.), n_D^{20} 1.4447, d_4^{20} 0.875 (Note 11), (Note 12),(Note 13), is collected. GC analysis (Note 14) shows this material to contain 3–5% of unidentified impurities with longer retention times (Note 15).

2. Notes

1. 2-Cyclohexen-1-one is easily prepared by a two-step procedure from cyclohexane-1,3-dione as described in *Org. Synth.*, **Coll. Vol. 5**, 294, 539, (1973). It is available from Fluka AG CH-9470 Buchs.
2. A brand name of this reagent is Merck Perhydrol.
3. To avoid loss of the volatile epoxide, removal of the dichloromethane on a rotary evaporator is not recommended.
4. GC analysis at 120° on a 2.2-m. column packed with 10% diethylene glycol succinate showed the forerun fraction to contain approximately 50% product. The other fraction is pure 2,3-epoxycyclohexanone.
5. The IR [($CHCl_3$) 1710 $cm.^{-1}$ strong (C=O)] and UV [(C_2H_5OH) max. 298 nm. (ε 15)] spectra demonstrate the absence of the enone system. ^1H NMR spectrum, δ (multiplicity, coupling constant J in Hz., number of protons): 1.5–3.0 (m, 6H), 3.32 (d, J = 4, 1H), 3.60 (m, 1H).
6. A further 1.06 g. (9.4%) of product may be obtained by Kugelrohr distillation of the residue.
7. This crude product does not show carbonyl absorption at 1710 $cm.^{-1}$ in the IR spectrum due to unreacted 2,3-epoxycyclohexanone.
8. If the crude hydrazone mixture is not be used immediately, it must be stored in a refrigerator.
9. (*E*)-Stilbene sublimes during the pyrolysis and may block a narrow aperture.
10. "Pract"-grade diethyl phthalate (obtainable from Fluka AG) should be redistilled at 126–129° (1 mm.) before use. It is stable under the reaction conditions and does not co-distil with 5-hexynal.
11. 5-Hexynal is very susceptible to air oxidation.
12. The product has the following IR spectrum $cm.^{-1}$: 3310 (C≡CH), 2725 (CH=O), 2115 (C≡C), 1720 (C=O).
13. Use of a Kugelrohr (70–80°, 30 mm.) is also satisfactory.
14. GC analysis was performed on a 2.2-m. 10% diethylene glycol succinate column at 80°.
15. The checkers found that GC analysis of one sample using a 3055 cm. by 0.3 cm. column packed with 10% SF-96 on Chromosorb P operated at 70° with a 60 ml./minute helium carrier gas flow rate gave five minor impurity peaks, two at shorter retention times, and three at longer retention times. None

of these impurities was present in greater than 1.1%; total impurities were 3%.

3. Discussion

2,3-Epoxycyclohexanone has been prepared in 30% yield[2] by epoxidation of 2-cyclohexen-1-one with alkaline hydrogen peroxide, using a procedure described for isophorone oxide (4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one).[3] A better yield (66%) was obtained using *tert*-butyl hydroperoxide and Triton B in benzene.[4] The procedure described here is simple and rapid.

The *N*-aminoaziridine version[5] of the α,β-epoxyketone→alkynone fragmentation is a possible alternative in situations where the simple tosylhydrazone version[6,7] fails. The tosylhydrazone method often gives good yields at low reaction temperatures, but it tends to be unsuccessful with the epoxides of acyclic enones or those not fully substituted at the β-carbon atom. For example, it has been reported[7] that 2,3-epoxycyclohexanone does not produce 5-hexynal by the tosylhydrazone route. The *N*-aminoaziridine method can also be recommended for the preparation of acetylenic aldehydes as well as ketones.

Both *trans*-1-amino-2,3-diphenylaziridine and 1-amino-2-phenylaziridine give α,β-epoxyhydrazones that fragment in the desired manner between 100° and 200°, the choice of reagent being dictated by the ease of separation of the alkynone from the by-products, (*E*)-stilbene and styrene, respectively. The diphenylaziridine is especially useful when the alkynone is relatively volatile and easily separable by distillation from (*E*)-stilbene, as is the case in the present example. The phenylaziridine is less bulky and more stable to acid than the diphenyl derivative, and may be tried with sterically hindered epoxyketones. The fragmentation is often run in an inert, high-boiling solvent to reduce resinification, but in many cases it can be achieved by pyrolysis of the neat, crude hydrazone with concomitant distillation of the product.

The limitations of the reaction have not been systematically investigated, but the inherent lability of the aziridines can be expected to become troublesome in the case of epoxyketones which do not readily undergo hydrazone formation. The use of acid catalysis is curtailed by the instability of the aziridines, particularly the diphenylaziridine, in acidic media. Because of their solvolytic lability, the hydrazones are best formed in inert solvents: a procedure proved helpful in some cases is to mix the aziridine and the epoxyketone in anhydrous benzene, then to remove the benzene on a rotary evaporator at room temperature; water formed in the reaction is thus removed as the azeotrope. This process is repeated, if necessary, until no carbonyl band remains in the IR spectrum of the residue.

Additional examples and a mechanistic discussion are available.[5] Borrevang[8] has reported a closely related fragmentation involving diazirine derivatives of cyclic α,β-epoxyketones.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 56

References and Notes

1. Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, CH-8006 Zürich, Switzerland.
2. H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).
3. R. L. Wasson and H. O. House, *Org. Synth.*, **Coll. Vol. 4**, 552 (1963).
4. N. C. Yang and R. A. Finnegang, *J. Am. Chem. Soc.*, **80**, 5845 (1958).
5. D. Felix, R. K. Müller, U. Horn, R. Joos, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 1276 (1972).
6. A. Eschenmoser, D. Felix, and G. Ohloff, *Helv. Chim. Acta*, **50**, 708 (1967); D. Felix, J. Schreiber, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 2896 (1971).
7. M. Tanabe, D. F. Crowe, R. L. Dehn, and G. Detre, *Tetrahedron Lett.*, 3739 (1967); M. Tanabe, D. F. Crowe, and R. L. Dehn, *Tetrahedron Lett.*, 3943 (1967).

8. P. Borrevang, J. Hjort, R. T. Rapala, and R. Edie, *Tetrahedron Lett.*, 4905 (1968).

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

hydrazone

Triton B

Benzene (71-43-2)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

2-propanol (67-63-0)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

styrene (100-42-5)

magnesium sulfate (7487-88-9)

aziridine (9002-98-6)

cyclohexane-1,3-dione (504-02-9)

diethyl phthalate (84-66-2)

Isophorone oxide,
4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one (10276-21-8)

helium (7440-59-7)

2-cyclohexen-1-one (930-68-7)

diethylene glycol succinate

N-aminoaziridine

1-Amino-2-phenylaziridine (19615-20-4)

tert-butyl hydroperoxide (75-91-2)

2,3-Epoxycyclohexanone (6705-49-3)

5-Hexynal (29329-03-1)

diphenylaziridine

phenylaziridine (696-18-4)

(E)-stilbene (103-30-0)

trans-1-Amino-2,3-diphenylaziridine (28161-60-6)

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