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of Reliable Methods
for the Preparation
of Organic Compounds

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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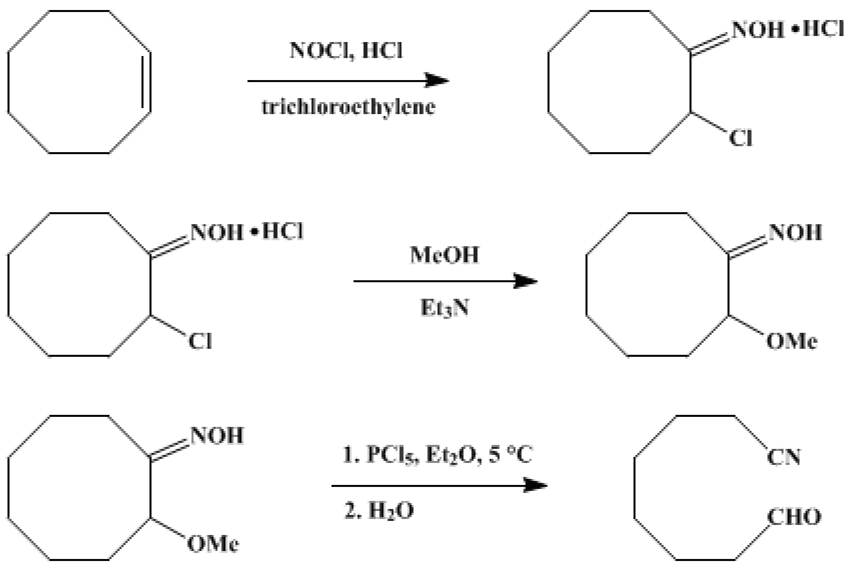
7-CYANOHEPTANAL

[Heptanal, 7-cyano-]



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Checked by E. J. Corey and I. Vlattas.

1. Procedure

A. *2-Chlorocyclooctanone oxime hydrochloride*. In a 2-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer, a gas inlet tube, and a tube fitted with a thermometer and a calcium chloride tube, is placed 55 g. (0.50 mole) of freshly distilled cyclooctene and 600 ml. of trichloroethylene. The solution is cooled with ice water to 5°, and 36 g. (0.55 mole) of nitrosyl chloride (Note 1) and excess of hydrogen chloride gas (about 400–600 ml. per minute) are bubbled into the solution, keeping the reaction temperature between 5–10°. The solution gradually becomes light reddish brown. The addition of nitrosyl chloride should be carried out in about 1.5 hours. After completion of the addition of nitrosyl chloride, hydrogen chloride gas is bubbled in for another 15 minutes. A light brown oily material is obtained after evaporation of the solvent under an aspirator pressure below 35° (Note 2) by using an efficient rotatory evaporator. On cooling this product in a refrigerator, 107.2 g. (*ca.* 100%) of crude 2-chlorocyclooctanone oxime hydrochloride is obtained as a solid.

B. *2-Methoxycyclooctanone oxime*. In a 500-ml., three-necked, round-bottomed flask, fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser equipped with a calcium chloride tube, is placed a solution of 53.5 g. (0.252 mole) of crude 2-chlorocyclooctanone oxime hydrochloride in 250 ml. of methanol. While cooling the vessel with running water, 60.7 g. of triethylamine (0.60 mole) is added dropwise during 40 minutes. The reaction temperature is kept below 50° and the reaction is continued for 30 minutes with stirring. After removal of methanol under reduced pressure using an efficient rotatory evaporator, a light brown semisolid is obtained; it is treated with 200 ml. of ether and 200 ml. of water to effect complete solution. The ether layer is separated and the aqueous layer is further extracted twice with ether. The combined ether solution is washed with saturated sodium chloride and dried over sodium sulfate. Removal of ether affords 42.8 g. of crude 2-methoxycyclooctanone oxime (Note 3) as a brown oil.

C. *Beckmann fission of 2-methoxycyclooctanone oxime.* In a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a calcium chloride tube is placed a suspension of 62.5 g. (0.30 mole) of phosphorus pentachloride (Note 4) in 150 ml. of absolute ether, and the reaction vessel is cooled with ice. A solution of 42.8 g. of crude 2-methoxycyclooctanone oxime

(0.25 mole) in 100 ml. of absolute ether is added over 30 minutes with vigorous stirring and the reaction is continued for 50 minutes at 5°. The reaction mixture, which becomes a transparent reddish brown solution (Note 5), is poured with mechanical stirring into 500 g. of ice in a 2-l. beaker. Stirring is continued for 1.5 hours at 5° (Note 6). The ether layer is separated and the aqueous layer is extracted with methylene chloride three times. The combined organic extracts are neutralized with dilute sodium carbonate solution and dried over sodium sulfate (Note 7). Removal of the solvent below 40° affords a reddish brown oil which is distilled to give 29.6 g. (85.2%) of 7-cyanoheptanal (Note 8), b.p. 109–115° (0.3 mm.) n^{26}D = 1.4456. The 2,4-dinitrophenylhydrazone has m.p. 74–75° after recrystallization from ethanol.

2. Notes

1. Solid nitrosyl chloride stored in a dry-ice box is quickly melted by warming, and as rapidly as possible the liquid nitrosyl chloride is weighed into a flask contained in a hood. Nitrosyl chloride is simply allowed to volatilize into the reaction from this flask under ambient conditions; rapid addition of nitrosyl chloride causes a decrease of the yield of α-chlorooxime. It may sometimes be necessary to control the rate of addition by cooling the nitrosyl chloride container with ice water.
2. 2-Chlorocyclooctanone oxime hydrochloride is unstable to heat. Therefore the temperature during removal of methanol should be kept below 35°.
3. The methanol-triethylamine reagent is superior to the previously used[2] methanolic sodium methoxide, and the crude 2-methoxycyclooctanone oxime thus obtained can be used for the Beckmann fission reaction without further purification. However, it is easily purified by distillation, b.p. 101° (0.7 mm.).
4. Thionyl chloride can also be used as the reagent for the Beckmann fission.
5. A very small amount of excess of phosphorus pentachloride is sometimes observed at the bottom of the reaction vessel.
6. If necessary, the temperature is kept at 5–10° by adding ice occasionally.
7. If the solution is acidic, the yield of ω-cyanoaldehyde is diminished by the occurrence of aldo condensation.
8. Although this distilled product, a pale yellow oil, is pure enough to use for most purposes, pure 7-cyanoheptanal, a colorless oil, is obtained by redistillation, b.p. 85–87° (0.013 mm.), n^{26}D 1.4451.

3. Discussion

The only preparation reported for 7-cyanoheptanal is that described by the submitters.[3] The present procedure starting from 2-methoxycyclooctanone oxime is superior to modifications employing 2-alkylamino- or 2-ethylthiocyclooctanone oxime in the Beckmann cleavage step.

ω-Cyanoaldehydes are not easily accessible by other routes but are interesting synthetic intermediates,[4] since the two terminal function groups are in different oxidation states which readily allow separate modification or elaboration.[5,6] The general applicability of the method described herein allows the synthesis of a wide variety of ω-cyanoaldehydes from available cycloolefins.

References and Notes

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5. E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).
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Appendix

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

2,4-dinitrophenylhydrazone

α-chlorooxime

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium methoxide (124-41-4)

methylene chloride (75-09-2)

nitrosyl chloride (2696-92-6)

trichloroethylene (79-01-6)

triethylamine (121-44-8)

7-Cyanoheptanal,
Heptanal, 7-cyano- (13050-09-4)

cyclooctene

2-Chlorocyclooctanone oxime hydrochloride

2-Methoxycyclooctanone oxime (10499-36-2)

2-ethylthiocyclooctanone oxime