



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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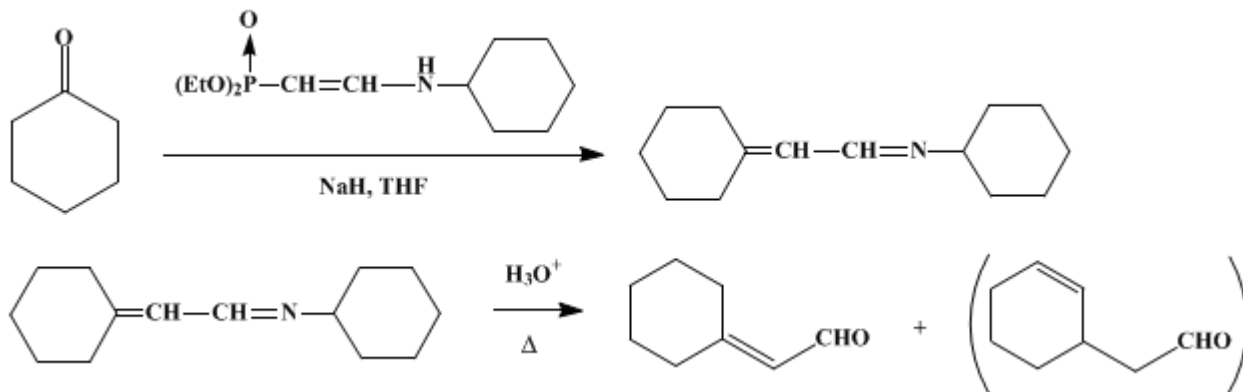
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.358 (1988); Vol. 53, p.104 (1973).

PREPARATION OF α,β -UNSATURATED ALDEHYDES *via* THE WITTIG REACTION: **CYCLOHEXYLIDENEACETALDEHYDE**

[Acetaldehyde, cyclohexylidene-]



Submitted by Wataru Nagata¹, Toshio Wakabayashi², and Yoshio Hayase¹.
Checked by Kyo Abe and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., three-necked, round-bottomed flask, fitted with a magnetic stirrer, dropping funnel, and nitrogen inlet is charged with 5.45 g. (0.116 mole) of sodium hydride (51% oil dispersion) (Note 1) and 30 ml. of dry tetrahydrofuran (Note 2). The system is flushed with nitrogen and a solution of 30.2 g. (0.116 mole) of diethyl 2-(cyclohexylamino)vinylphosphonate [*Org. Synth., Coll. Vol. 6*, 448 (1988)] in 90 ml. of dry tetrahydrofuran is added dropwise to the stirred mixture over a period of 15 minutes. During the addition the temperature is maintained at 0–5° with an ice bath. The mixture is stirred for an additional 15 minutes at 0–5° to ensure complete reaction. A solution of 10.3 g. (0.105 moles) of cyclohexanone (Note 3) in 70 ml. of dry tetrahydrofuran is added dropwise to the mixture over a period of 20 minutes, so that the temperature does not exceed 5°. The mixture is stirred for an additional 90 minutes at 20–25° in a water bath. During the stirring a gummy precipitate of sodium diethyl phosphate is observed. The mixture is poured into 500 ml. of cold water and extracted with three 300-ml. portions of diethyl ether. The combined ether extracts are washed twice with 200 ml. of saturated aqueous salt solution, dried over anhydrous sodium sulfate, and distilled under reduced pressure (35 mm.) at 25–30°. The residue is dissolved in 300 ml. of benzene and transferred to a 3-l., three-necked, round-bottomed flask equipped with a stirrer and a reflux condenser. To this solution is added a solution of 72 g. (0.57 mole) of oxalic acid dihydrate in 900 ml. of water (Note 4). The stirred mixture is refluxed for 2 hours under nitrogen, cooled, and transferred to a separatory funnel. The aqueous layer is extracted with two 300-ml. portions of ether. The combined organic extracts are washed with 200 ml. of water, then with 200 ml. of saturated aqueous salt solution, and dried over anhydrous sodium sulfate, and distilled under reduced pressure (35 mm.) at 25–30°. The residue is transferred to a 30-ml., round-bottomed flask and distilled under reduced pressure through a 5-cm. Vigreux column, yielding 10.8 g. (83%, (Note 5)) of cyclohexylideneacetaldehyde, b.p. 78–84° (12 mm.), containing *ca.* 15% of the isomeric cyclohexenylacetaldehyde (Note 6).

2. Notes

1. Sodium hydride (50–51% in mineral oil) was purchased from Metal Hydrides Inc. and used as 51%.
2. Reagent grade tetrahydrofuran was freshly distilled over sodium hydride before use. The checkers used lithium aluminum hydride to dry the solvent [see *Org. Synth., Coll. Vol. 5*, 976 (1973) for warning note].
3. Reagent grade cyclohexanone was redistilled.
4. When a more concentrated solution (72 g. of oxalic acid in 450 ml. of water) was used, the product contained larger amounts of the β,γ -isomer, cyclohexenylacetaldehyde. To suppress this double bond isomerization, a 4–7% aqueous oxalic acid solution was used.
5. The yields were 80–85% in several runs.
6. The submitters found that analysis of the final product by GC indicated a 15% contaminant of the by-product, cyclohexenylacetaldehyde. The analysis was conducted on a column packed with 5% XE-60 on Chromosorb W at 120°. The retention times for cyclohexenylacetaldehyde and cyclohexylideneacetaldehyde were 1.3 and 3.3 minutes, respectively. The checkers found that the product contained 10–15% of cyclohexenylacetaldehyde by GC analysis and 12–16% by NMR spectral analysis (CDCl_3), using the relative intensity of two signals (δ 9.53 and 9.97) due to the aldehydic protons of the two compounds. Reported physical constants are b.p. 58–62° (16 mm.) for cyclohexenylacetaldehyde and b.p. 80–85° (16 mm.) for cyclohexylideneacetaldehyde.³

3. Discussion

For the conversion of ketones into α,β -unsaturated aldehydes containing two additional carbon atoms, several multistep processes *via* ethynyl or vinyl carbinol intermediates have been reported.^{3,4,5,6,7,8,9} Although the overall yields obtained by these routes for the conversion of cyclohexanone into cyclohexylideneacetaldehyde have never exceeded 50%, they were the only useful methods for this type of conversion until the Wittig^{10,11} method appeared. This process consists of the normal aldol condensations of ketones with the lithium salt of ethylidenecyclohexylamine, followed by dehydration and hydrolysis.

The present procedure also illustrates an excellent, general method for the conversion of ketones and aldehydes¹² into the corresponding α,β -unsaturated aldehydes, using diethyl 2-(cyclohexylamino)vinylphosphonate.¹³ The yield is usually high, and the reaction proceeds stereoselectively, affording only the *trans* isomer. In the reaction of 3-ketosteroids with this reagent, no β,γ -isomers were formed.¹² Recently Meyers and co-workers¹⁴ reported a new method for the synthesis of α,β -unsaturated aldehydes.

A remarkable improvement of the present procedure, involving the *in situ* preparation of a solution of the lithium salt of diethyl 2-(*tert*-butylamino)vinylphosphonate¹³ followed by addition of an aldehyde or a ketone, has recently been reported.¹⁵

References and Notes

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

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

Cyclohexanone (108-94-1)

vinyl carbinol (107-18-6)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

oxalic acid dihydrate (6153-56-6)

cyclohexenylacetaldehyde

ethylidenecyclohexylamine (1193-93-7)

Diethyl 2-(cyclohexylamino)vinylphosphonate (20061-84-1)

sodium diethyl phosphate

Cyclohexylideneacetaldehyde,
Acetaldehyde, cyclohexylidene- (1713-63-9)

lithium salt of diethyl 2-(tert-butylamino)vinylphosphonate