Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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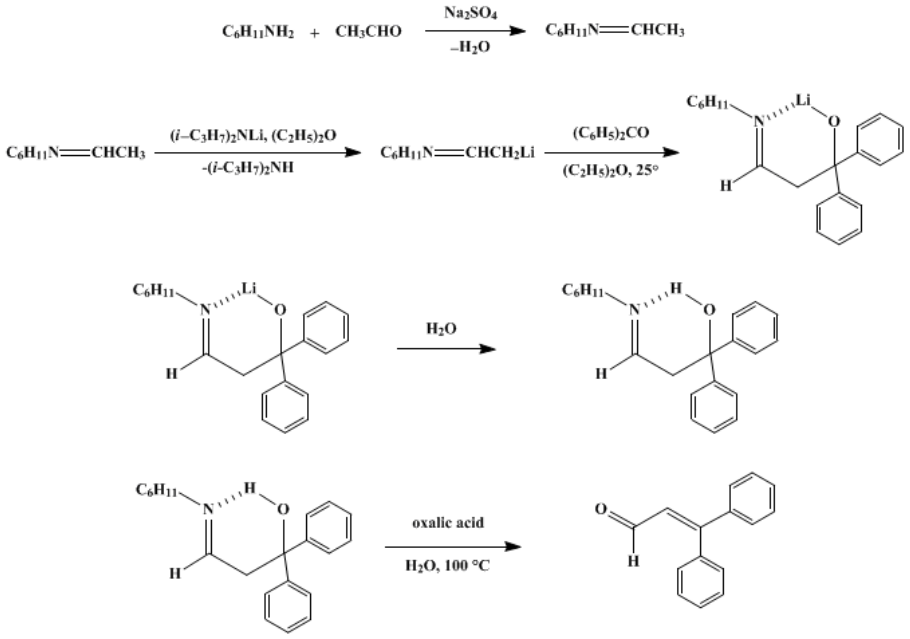
DIRECTED ALDOL CONDENSATIONS: β-PHENYLCINNAMALDEHYDE

[2-Propenal, 3,3-diphenyl-]



Submitted by G. Wittig[1] and A. Hesse.
Checked by Allan Y. Teranishi and Herbert O. House.

1. Procedure

A. N-*Ethylidenecyclohexylamine*. A dry, 500-ml., round-bottomed flask fitted with a magnetic stirrer is flushed with nitrogen and stoppered with a rubber septum. With a hypodermic syringe 99.2 g. (1.00 mole) of freshly distilled cyclohexylamine (b.p. 133–134°) is added to the flask. After the amine has been cooled to approximately −20° (Note 1) with an acetone–dry ice bath, 44.1 g. (1.00 mole) of freshly distilled acetaldehyde (b.p. 21°) is added from a hypodermic syringe dropwise and with stirring over a 15-minute period. During the initial phase of this addition a white solid separates but redissolves as the addition is continued. The resulting cold solution is stirred at −20° for approximately 45 minutes, at which time a large amount of white solid separates and further stirring is impractical. The resulting mixture is allowed to stand at −20° for 15 minutes before 15 g. of anhydrous sodium sulfate is added and the mixture is allowed to melt and warm to room temperature. The resulting mixture is gravity filtered, and the residue is washed with approximately 15 ml. of diethyl ether. The combined filtrates are dried over 5 g. of anhydrous magnesium sulfate and filtered. The filtrate is distilled under reduced pressure, separating 95–99 g. (76–79%) of *N*-ethylidenecyclohexylamine as a colorless liquid, b.p. 47–48° (12 mm.) or 54–55° (16 mm.), n_D^{20} 1.4579; n_D^{25} 1.4560. This product should either be used immediately in the next step or stored in a refrigerator (5–10°) under a nitrogen atmosphere.

B. N-(3-*Hydroxy*-3,3-*diphenylpropylidene)cyclohexylamine*. A dry, 250-ml., round-bottomed flask or dry 250-ml. Schlenk tube fitted with a magnetic stirrer is flushed with oxygen-free nitrogen (Note 2), stoppered with a rubber septum, and cooled in an ice bath. A slight positive pressure of oxygen-free nitrogen (Note 2) is maintained in the vessel throughout the reaction with a nitrogen line connected both to a pressure relief valve and a hypodermic needle which is inserted through the rubber septum. With a hypodermic syringe a solution of 2.53 g. (3.60 ml. or 0.0250 mole) of pure diisopropylamine (Note 3) in 25 ml. of absolute ether (Note 4) is added to the cold reaction vessel. An ethereal solution containing 0.025 mole of methyllithium (Note 5) is added from a hypodermic syringe dropwise and with stirring. During this addition a vigorous evolution of methane is observed. After the solution of lithium diisopropylamide has been stirred at 0° for 5–10 minutes a negative Gilman color test[2] for methyllithium is obtained. A solution of 3.13 g. (0.0250 mole) of *N*-ethylidenecyclohexylamine in 20 ml. of absolute ether (Note 4) is added from a hypodermic syringe, dropwise and with stirring, to the cold (0°) solution of lithium diisopropylamide, and the resulting solution is stirred for 10 minutes (Note 6). This solution is then cooled to −70° with a methanol–dry ice bath, and a solution of 4.55 g. (0.0250 mole) of benzophenone in 25 ml. of absolute ether is added to the cold (−70°) reaction vessel with a hypodermic syringe. The resulting solution is allowed to warm to room temperature and stand for 24 hours, during which time a white solid separates. The reaction mixture is cooled to 0° in an ice bath, treated with approximately 50 ml. of water, and stirred at 0° for 30 minutes. The cold mixture is filtered with suction, removing the white crystalline product, and the organic phase from the filtrate is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The combined residues from the filtration and concentration of the organic phase of the filtrate are recrystallized from hexane, separating 6.80–7.06 g. (89–92%) of *N*-(3-hydroxy-3,3-diphenylpropylidene)cyclohexylamine as white needles, m.p. 127–128° (Note 7).

C. β-*Phenylcinnamaldehyde*. A mixture of 1.54 g. (0.00520 mole) of *N*-(3-hydroxy-3,3-diphenylpropylidene)cyclohexylamine and 10 g. (0.11 mole) of oxalic acid is subjected to steam distillation, which is continued until a clear distillate is obtained; this requires about 2 hours. The steam distillate is extracted with two 25-ml. portions of ether, and the combined ethereal extracts are dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual crude product (approximately 1.0 g., m.p. 42–44°) is recrystallized from pentane, yielding 0.80–0.88 g. (78–85%) of β-phenylcinnamaldehyde as pale yellow needles, m.p. 46–47° (Note 8).

2. Notes

1. The amine (m.p. −21°) should be cooled with stirring until it just begins to freeze. At this point the temperature of the external cooling bath should be maintained at −20° by the periodic addition of pieces of dry ice.

2. One suitable arrangement for the purification of nitrogen is described by H. Metzger and E. Müller.[3] The checkers used a prepurified grade of nitrogen without further purification.

3. Diisopropylamine (b.p. 83–84°, available from Fluka AG or from Eastman Organic Chemicals) was purified by refluxing it over either sodium wire or sodium hydride for approximately 30 minutes, then distilling the amine into a dry receiver under a nitrogen atmosphere. Because of the relatively low boiling point of the amine, a dispersion of sodium hydride in mineral oil, available from Metal Hydrides, Inc., Beverly, Massachusetts, can be used directly in this purification without prior removal of the mineral oil.

4. The submitters purified the ether by refluxing it over sodium wire until the blue color of benzophenone ketyl persisted when benzophenone was added, and distilling the ether into a dry receiver under a nitrogen atmosphere. The checkers further purified an

absolute grade of ether obtained from Mallinckrodt Chemical Works by distilling it from lithium aluminum hydride under a nitrogen atmosphere.

5. An ethereal solution of methyllithium may be prepared in the following manner. A dry, 1-l., three-necked flask is fitted with a magnetic stirrer, a gas-inlet tube, and a dry ice reflux condenser. In the flask are placed 800 ml. of absolute ether (Note 4) and 16 g. (2.3 g.-atoms) of pieces of lithium wire. Over a period of 4–5 hours, 100 g. (1.05 moles) of methyl bromide is distilled into the reaction flask with continuous stirring. The resulting mixture is stirred for an additional hour and allowed to stand overnight under a nitrogen atmosphere, permitting the insoluble particles to settle. The supernatant liquid is transferred under a nitrogen atmosphere to a dry storage buret or some other dry vessel capped with a rubber septum. Alternatively, an ethereal solution of methyllithium may be purchased from Foote Mineral Co., Exton, Pennsylvania.

Aliquots of the methyllithium solution should be removed from the storage buret or storage vessel for standardization. The checkers employed the titration procedure of Watson and Eastham [*Org. Synth.*, **Coll. Vol. 5**, 211 (1973)][4] with either 2,2'-dipyridyl or *o*-phenanthroline as an indicator for standardizing the methyllithium solution.

6. When an aliquot of this solution is subjected to a Gilman color test,[2] a wine-red color is obtained.

7. The product has IR absorption ($CHCl_3$) at 3250 (broad, associated OH) and 1665 $cm.^{-1}$ (C=N) with ^1H NMR peaks ($CDCl_3$) at δ 1.0–3.0 (m, 11H, C_6H_{11}), 3.12 (d, *J* = 4 Hz., 2H, CH_2), 7.0–7.7 (m, 10H, $2C_6H_5$), and 7.78 (t, *J* = 4 Hz., 1H, C*H*=N).

8. The product has IR absorption (CCl_4) at 2720, 2745, and 2840 $cm.^{-1}$ (aldehyde CH) and at 1675 cm^{-1} (conjugated C=O) with UV maxima (95% C_2H_5OH) at 224 nm (ε 13,500) and 300 nm (ε 16,500) and ^1H NMR peaks (CCl_4) at δ 6.22 (d, *J* = 8 Hz., 1H, C*H*), 7.1–7.5 (m, 10H, $2C_6H_5$), and 9.40 (d, *J* = 8 Hz., 1H, C*H*O).

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3. Discussion

Until recently it has not been possible to control the aldol condensation;[5] the enolate anion derived from an aldehyde could not be condensed with a carbonyl group of a ketone, because of the rapidity of the self-condensation of the aldehyde. This problem can be circumvented if the aldehyde is first converted to the corresponding azomethine derivative. The anion derived from this "protected" aldehyde can be added to another carbonyl group, giving an easily crystallized β-hydroxy imine adduct. Subsequent dehydration and concurrent removal of the imino protecting group yields an α,β-unsaturated aldehyde. The overall procedure, utilizing an organometallic intermediate, constitutes a new method for effecting an aldol condensation. With reaction conditions illustrated in this preparation other carbonyl compounds with acidic α-hydrogens, such acetone or β-ionone, can also be used, because the deprotonation of the carbonyl compound by the metalated Schiff base is largely suppressed. This directed aldol condensation is useful for the preparation of naturally occurring α,β-unsaturated carbonyl compounds or intermediates useful in the syntheses of these substances.[6] The method can also be applied to the synthesis of α,β-unsaturated ketones if a ketimine is used as the azomethine component in the condensation.[6] Although the condensation is also successful with acetaldimine derivatives which contain one α-alkyl substituent, only very poor yields of condensation products are obtained when two α-alkyl substituents are present.[6] This limitation is possibly the result rate of a retarded rate of proton abstraction from the imine, due to the steric hindrance offered by the α-alkyl substituents.[7]

Although the reaction of aldehydes with β-carbonylmethylene phosphoranes constitutes a good synthetic route to α,β-unsaturated carbonyl compounds,[8,9,10,11] this procedure is normally not applicable to ketones. This limitation has recently been overcome by the reaction of ketones with the cyclohexylimine derivative of β-carbonylmethylenephosphonates.[12]

With the aid of the directed aldol condensation procedure, *N*-(3-hydroxy-3,3-diphenylpropylidene)cyclohexylamine has been prepared for the first time. Previous methods employed for the synthesis of β-phenylcinnamaldehyde include the application of the Sommelet reaction to 3,3-diphenylallyl bromide with isolation of the aldehyde as its semicarbazone,[13] the reaction of β,β-diphenylvinylmagnesium bromide with *N*-methylformanilide followed by hydrolysis,[14] and the reaction of this same Grignard reagent with ethyl orthoformate followed by hydrolysis of the resulting acetal.[15] This unsaturated aldehyde has also been prepared by the formylation of 1,1-diphenylethylene with *N*-methylformanilide and phosphorus oxychloride,[16] by the oxidation of β-phenylcinnamyl alcohol with manganese dioxide,[17] and by the rearrangement of 1,1-diphenyl-2-propyn-1-ol in an ethylene glycol solution containing boron trifluoride and mercury(II) oxide, followed by hydrolysis of the intermediate acetal.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 121
- Org. Syn. Coll. Vol. 6, 571
- Org. Syn. Coll. Vol. 6, 666
- Org. Syn. Coll. Vol. 6, 692
- Org. Syn. Coll. Vol. 7, 172
- Org. Syn. Coll. Vol. 7, 346

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References and Notes

1. Institut für Organische Chemie, Universität Heidelberg, Heidelberg, Germany.
2. H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).
3. H. Metzger and E. Müller, in "Methoden der organischen Chemie" (Houben-Weyl), 4th ed., E. Müller, Ed., Vol 1/2, George Thieme Verlag, Stuttgart, 1959, p. 327.
4. S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
5. A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).
6. G. Wittig and P. Suchanek, *Tetrahedron*, **22**, 347 (1966).

7. H. Reiff, Dissertation, Universität Heidelberg, 1966.
8. S. Trippett and D. M. Walker, *J. Chem. Soc.*, **1961**, 1266.
9. H. Takahashi, K. Fujiwara, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **35**, 1498 (1962).
10. A. K. Bose and R. T. Dahill, Jr., *J. Org. Chem.*, **30**, 505 (1965).
11. A. Maercker, *Org. React.*, **14**, 270 (1965).
12. W. Nagata and Y. Hayase, *Tetrahedron Letters*, **1968**, 4359.
13. K. Ziegler and P. Tiemann, *Ber. Dtsch. Chem. Ges.*, **55**, 3406 (1922).
14. G. Wittig and R. Kethur, *Ber. Dtsch. Chem. Ges.*, **69**, 2078 (1936).
15. E. P. Kohler and R. G. Larsen, *J. Am. Chem. Soc.*, **57**, 1448 (1935).
16. H. Lorenz and R. Wizinger, *Helv. Chim. Acta*, **28**, 607 (1945).
17. R. Heilmann and R. Glenat, *Bull. Soc. Chim. Fr.*, [5] **22**, 1586 (1955).
18. H. Siemer and K. Stack, Ger. Pat. 1,001,674 [*Chem. Abstr.*, **54**, 1454 (1960)].
19. G. Wittig, H. Pommer, and W. Stilz, Ger. Pat. 1,199,252 [*Chem. Abstr.*, **63**, 1739 (1965)].
20. G. Wittig and H. D. Frommeld, *Chem. Ber.*, **97**, 3548 (1964).
21. G. Wittig, H. D. Frommeld, and P. Suchanek, *Angew. Chem. Int. Ed. Engl.*, **2**, 683 (1963);
22. G. Wittig and H. Reiff, *Angew, Chem., Int. Ed. Engl.*, **7**, 7 (1968);
23. G. Wittig, *Rec. Chem. Prog.*, **28**, 45 (1967).

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

benzophenone ketyl

rubber septum

o-phenanthroline

acetaldehyde (75-07-0)

ether,
diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

mercury(II) oxide (21908-53-2)

Phosphorus Oxychloride (21295-50-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

ethylene glycol (107-21-1)

methyl bromide (74-83-9)

manganese dioxide (1313-13-9)

1,1-Diphenylethylene (530-48-3)

Pentane (109-66-0)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

boron trifluoride (7637-07-2)

cyclohexylamine (108-91-8)

lithium aluminum hydride (16853-85-3)

N-methylformanilide (93-61-8)

sodium hydride (7646-69-7)

hexane (110-54-3)

Methyllithium (917-54-4)

N-Ethylidenecyclohexylamine (1193-93-7)

2,2'-dipyridyl (366-18-7)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

β-Phenylcinnamaldehyde,
2-Propenal, 3,3-diphenyl- (1210-39-5)

3,3-diphenylallyl bromide

β,β-diphenylvinylmagnesium bromide

β-phenylcinnamyl alcohol

1,1-diphenyl-2-propyn-1-ol (3923-52-2)

N-(3-Hydroxy-3,3-diphenylpropylidene)cyclohexylamine (1235-46-7)