Organic Syntheses

A Publication
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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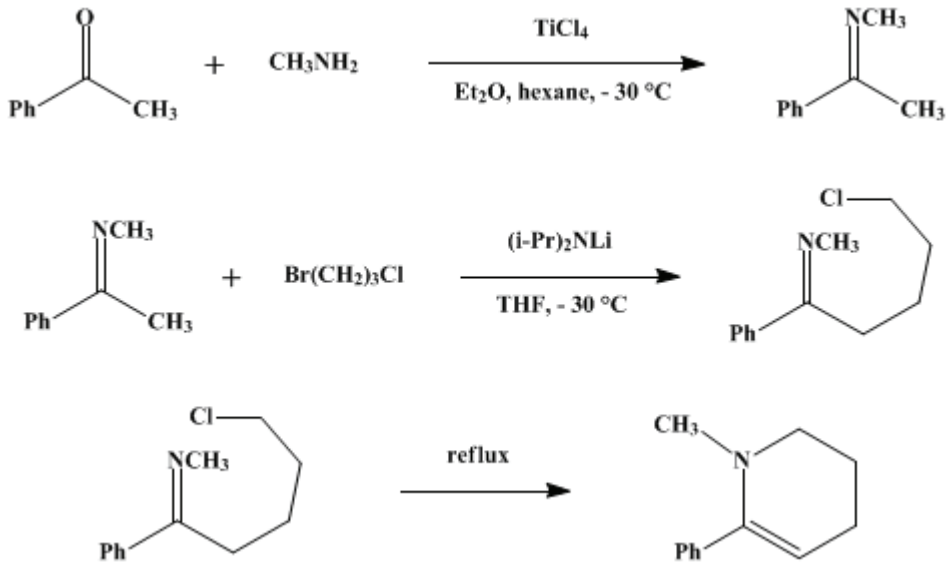
ENDOCYCLIC ENAMINE SYNTHESIS: *N*-METHYL-2-PHENYL-Δ²-TETRAHYDROPYRIDINE

[Pyridine, 1,2,3,4-tetrahydro-1-methyl-5-phenyl-]



Submitted by D. A. Evans[1] and L. A. Domeier.
Checked by R. Decorzant and G. Büchi.

1. Procedure

[2]

A. N-(α-*Methylbenzylidene*)*methylamine*. Approximately 70 ml. of methylamine, passed through a potassium hydroxide trap, is condensed into a dry, premarked, nitrogen-purged, 1-l. flask (Note 1) equipped with a mechanical stirrer, an acetone–dry ice condenser with drying tube, and a 250-ml., pressure-equalizing addition funnel topped by a gas-inlet connection. The flask is cooled in a methanol–ice bath, and a solution of 48 g. (0.40 mole) of acetophenone (Note 2) in 200 ml. of dry diethyl ether (Note 3) is added through the addition funnel. The addition funnel is rinsed with 25 ml. of dry ether, purged with nitrogen, and charged with 220 ml. of 1 *M* titanium tetrachloride in hexane (Note 4), which is added to the cooled flask over a 1.5-hour period (Note 5). After stirring an additional 30 minutes in the methanol–ice bath and 30 minutes at room temperature, the mixture is filtered through a Büchner funnel into a 1-l., round-bottomed flask (Note 6), and the solid material is rinsed with an additional 100 ml. of ether. The solvents are removed on a rotary evaporator, and the yellow residue is transferred to a 100 ml. round-bottomed flask. Distillation through a short, vacuum-jacketed, Vigreux column yields 37–47 g. (70–88%) of the colorless imine, b.p. 93–95° (11 mm.) (Note 7) and (Note 8).

B. N-*Methyl*-2-*phenyl*-Δ²-*tetrahydropyridine*. A 500-ml., nitrogen-purged flask equipped with serum cap, reflux condenser with nitrogen inlet connection, thermometer, and stirring bar, is charged with 100 ml. of dry tetrahydrofuran (Note 9) and 21.0 ml. (0.155 mole) of diisopropylamine (Note 10). The solution is cooled to −30° with an acetone bath to which dry ice was added as needed, and 72.4 ml. (0.155 mole) of 2.14 *M* *n*-butyllithium in hexane (Note 11) is added while keeping the temperature below 0°. After cooling the mixture to −40°, 20.6 g. (0.155 mole) of the imine (from part A) is added *via* syringe over a period of about 2 minutes. The resulting yellow solution is maintained at −40° to −30° for 15 minutes then cooled to −60°. To the cold solution is added 25.2 g. (16.5 ml., 0.160 mole) of 1-bromo-3-chloropropane (Note 12) in one portion *via* syringe while the temperature is maintained below −40°. The reaction mixture is maintained between −60° and −50° for 5 minutes, the bath is removed, and the mixture is allowed to warm to room temperature. The reaction mixture is refluxed 3

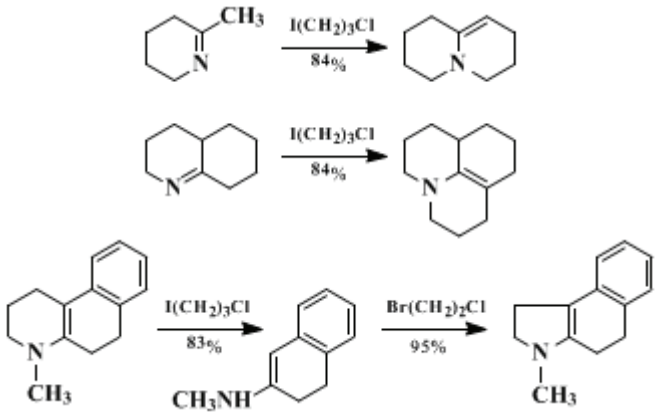
hours to effect ring closure (Note 13). After the addition of 150 ml. of 10% aqueous potassium carbonate to the cooled solution, the reaction mixture is stirred several minutes and transferred to a nitrogen-purged separatory funnel. The reaction flask is rinsed with 100 ml. of 1 : 1 benzene–ether which is added to the separatory funnel, and the entire mixture is diluted with 150 ml. of water. After shaking, the aqueous layer is removed, the organic layer is washed with 100 ml. of brine, shaken with anhydrous granular sodium sulfate, and filtered into a 1-l., round-bottomed flask. The solvents are removed on a rotary evaporator, and the residue is transferred to a 100-ml., round-bottomed flask. Short-path distillation under high vacuum yields 18.8–21.7 g. (70–81%) of pale yellow enamine, b.p. 87–88° (4 mm.) (Note 14) and (Note 15).

2. Notes

1. All three necks of the flask should be vertical and not set at an angle, preventing the accumulation of large amounts of the methylamine complex of titanium tetrachloride on the sides of the reaction flask.
2. Acetophenone was purchased from Matheson, Coleman and Bell and used without further purification.
3. Anhydrous ether available from Mallinckrodt Chemical Co. can be used without further drying.
4. Titanium tetrachloride (purified grade) was purchased from J. T. Baker. A 1 *M* titanium tetrachloride solution was prepared by diluting 55 ml. of titanium tetrachloride (1.73 g./ml.) to a volume of 500 ml. with hexane which had been passed through 40–50 g. of basic alumina (Activity I).
5. The addition funnel should be thoroughly, but gently, flushed with nitrogen before being charged with the titanium tetrachloride solution. A slight flow of nitrogen should be maintained throughout the addition, preventing the diffusion of methylamine into the funnel where it will form a red insoluble titanium tetrachloride–amine complex.
6. If done quickly, the filtration need not be done under nitrogen, with no effect on the yield in the case of this particular imine.
7. ^{1}H NMR (CCl_4): 2.1 (s, 3H, NCH_3), 3.2 (s, 3H, vinylic CH_3), 7.2 (m, 3H, aryl C*H*), 7.7 (m, 2H, aryl C*H*). IR (CCl_4) cm.$^{-1}$: 1645, 1450, 1370, 1290. Purity was confirmed by GC on a 4-ft., 10% Carbowax 20 *M* column at 165°.
8. The imine should be stored under nitrogen and exposed to the air as little as possible during handling.
9. Tetrahydrofuran was freshly distilled from lithium aluminum hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for a note concerning the hazards involved in purifying tetrahydrofuran.
10. Diisopropylamine was purchased from Aldrich Chemical Co. and distilled from calcium hydride prior to use.
11. *n*-Butyllithium in hexane was purchased from Ventron Corp.
12. 1-Bromo-3-chloropropane was purchased from Matheson, Coleman and Bell and distilled from phosphorus pentoxide prior to use.
13. If the mixture is not refluxed, the intermediate imine may be isolated.
14. ^{1}H NMR (CCl_4): 1.5–2.1 (m, 4H, 2CH_2), 2.4 (s, 3H, NCH_3), 3.0 (m, 2H, NCH_2), 4.8 (t, J = 4 Hz., 1H, vinylic C*H*), 7.3 (m, 5H, C_6H_5). IR (CCl_4) cm^{-1}: 1640, 1605, 1500, 1460, 1375, 1360, 1130, 1040. Purity was confirmed by GC on a 4-ft., 10% Carbowax 20 M column at 165°.
15. The enamine should be refrigerated under nitrogen and used within a few days.

3. Discussion

N-Methyl-2-phenyl-Δ^2-tetrahydropyridine and similar compounds have previously been prepared by the hydrolysis and decarboxylation of α-benzoyl-*N*-methyl-2-piperidone[3] and by the addition of phenyl Grignard reagents to *N*-methyl-2-piperidone, followed by dehydration.[4] Both of these methods require that a heterocyclic ring already be present in the system. In contrast, this procedure offers a new, flexible route to the construction of five- or six-membered heterocyclic rings which may easily be incorporated into larger polycyclic products. Several examples[5] of this process demonstrate this utility:



A wide variety of more complex endocyclic enamines are thus made available as synthetic intermediates.

References and Notes

1. Department of Chemistry, University of California, Los Angeles, California 90024. [Present address: Division of Chemistry and Chemical Engineering, The Chemical Laboratories, California Institute of Technology, Pasadena, California 91125].
2. This procedure is based on the work of Weingarten: H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967).
3. K. H. Büchel, H. J. Schulze-Steinem, and F. Korte, U. S. Pat. 3,247,213 (1966); K. H. Büchel and F. Korte, *Chem. Ber.*, **95**, 2438 (1962).
4. R. Lakes and O. Grossmann, *Coll. Czech. Commun.*, **8**, 533 (1936).
5. D. A. Evans, *J. Am. Chem. Soc.*, **92**, 7593 (1970).

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

alumina

brine

N-Methyl-2-phenyl-Δ^2-tetrahydropyridine

methylamine complex of titanium tetrachloride

potassium carbonate (584-08-7)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

1-bromo-3-chloropropane (109-70-6)

methylamine (74-89-5)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

calcium hydride (7789-78-8)

diisopropylamine (108-18-9)

titanium (7440-32-6)

Pyridine, 1,2,3,4-tetrahydro-1-methyl-5-phenyl-

phosphorus pentoxide (1314-56-3)

α-benzoyl-N-methyl-2-piperidone

N-methyl-2-piperidone (931-20-4)

N-(α-Methylbenzylidene)methylamine (6907-71-7)