Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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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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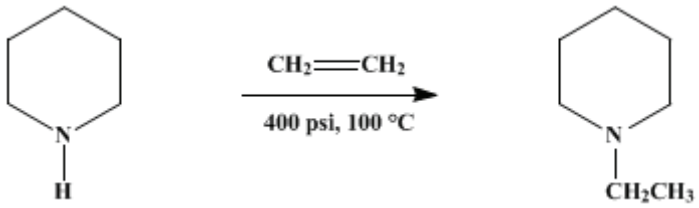
N-ETHYLPIPERIDINE

[Piperidine, 1-ethyl-]



Submitted by J. Wollensak and R. D. Closson[1].
Checked by C. D. Ver Nooy and B. C. McKusick.

1. Procedure

A 1-l. three-necked flask equipped with a reflux condenser, an inlet for dry nitrogen, and a mechanical stirrer is flushed with dry nitrogen. It is then charged with 340 g. (4.00 moles) of piperidine (Note 1) 4.4 g. (0.19 g. atom) of sodium, and 5.0 g. (5.1 ml., 0.063 mole) of pyridine (Note 2). While a slow stream of nitrogen continues to pass through the flask, the solution is heated under reflux with high-speed stirring for approximately 10 minutes. During this time most of the sodium reacts without evolution of hydrogen, and the dispersion darkens. The dispersion, which contains some finely divided solids, is cooled and transferred to a 2-l. stirred autoclave (Note 3) under nitrogen. An additional 85 g. (1.00 mole) of piperidine is used to wash the last portions of the dispersion into the autoclave.

The autoclave is pressured with ethylene (Note 2) to 400 lb./in.^{2} with stirring (Note 4). It is then heated to 100° with stirring, which causes the pressure to rise to about 555 lb./in.^{2}. It is maintained at 100° with stirring until a gradual drop in pressure ceases; this usually takes about 2.5 hours, but it may take as long as 10 hours (Note 5). The autoclave is cooled to room temperature, and the excess ethylene is vented. The reaction mixture is transferred to a 1-l. round-bottomed flask, the autoclave is rinsed with 100 ml. of methanol that is added to the flask, and the mixture is fractionated through a 90-cm. column packed with glass helices. After a fore-cut of 50–100 g. distilling at 55–129°, 434–468 g. (77–83%) of N-ethylpiperidine is collected; b.p. 129–130.5°; n_D^{20} 1.443–1.444 (Note 6).

2. Notes

1. Piperidine obtained from Eastman Kodak was fractionated through a 90-cm. column packed with glass helices, and the fraction distilling at 105° was used for this work. This material contained approximately 0.36 wt.% of pyridine as indicated by vapor phase chromatography and ultraviolet analysis.
2. Sodium from Ethyl Corporation, pyridine from Eastman Kodak, and C.P. ethylene from Matheson are suitable.
3. The kind of stirrer is not important. The submitters obtained similar results with a three-blade propeller turning at 600 r.p.m. and a paddle stirrer turning at 78 r.p.m. They believe that a rocking autoclave could be substituted for a stirred one.
4. Over half the ethylene pressured into the autoclave dissolves in the piperidine. It is essential to agitate the piperidine during the pressuring operation so that the piperidine will become saturated with ethylene, for otherwise there will not be enough ethylene for the reaction.
5. The checkers found that it shortened the reaction time appreciably to repressure the autoclave to 400–500 lb./in.^{2} whenever the pressure dropped below 350 lb./in.^{2}
6. The checkers got the same results using half the quantities of reactants in a 1-l. stirred autoclave.

3. Discussion

The described procedure is essentially the method of Closson, Kolka, and Ligett.[2] Since N-ethylpiperidine was first prepared by Cahours by reaction of piperidine with ethyl iodide,[3] a large number of synthetic methods have been used for its preparation. Reductive alkylation of pyridine with ethanol over Langenback or Raney nickel catalyst gives N-ethylpiperidine in high yield.[4] The compound may similarly be prepared by catalytic hydrogenation of N-ethylpyridinium chloride with platinum oxide as catalyst[5] and by the alkylation of piperidine using ethanol and Raney nickel catalyst under hydrogenating conditions.[6] Other methods that have been used are electrolytic reduction of N-ethylglutarimide,[7] interaction of pentamethylene oxide and ethylamine at high temperature over aluminum oxide,[8] interaction of ethylamine and 1,5-dibromopentane,[9] and reduction of 1-acetylpiperidine with lithium aluminum hydride.[10]

4. Merits of the Preparation

The procedure is illustrative of a general method of ethylating amines, wherein one reacts the amine with ethylene using an alkali-metal salt of the amine as catalyst.[2] Di-*n*-butylamine and *n*-hexylamine have been thus ethylated at 130–160°, aniline, *o*-toluidine, and N-methylaniline at 240–275°. In general, higher olefins add to amines only sluggishly.[2]

References and Notes

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

Ethyl Corporation

ethanol (64-17-5)

methanol (67-56-1)

aniline (62-53-3)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

platinum oxide

Raney nickel (7440-02-0)

pyridine (110-86-1)

sodium (13966-32-0)

piperidine (110-89-4)

1,5-dibromopentane (111-24-0)

ethylene (9002-88-4)

pentamethylene oxide (142-68-7)

Ethyl iodide (75-03-6)

aluminum oxide (1344-28-1)

N-Methylaniline (100-61-8)

lithium aluminum hydride (16853-85-3)

ethylamine (75-04-7)

di-n-butylamine (111-92-2)

N-Ethylpiperidine,
Piperidine, 1-ethyl- (766-09-6)

N-ethylpyridinium chloride

N-ethylglutarimide

1-acetylpiperidine (618-42-8)

o-toluidine (95-53-4)

n-hexylamine (111-26-2)