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.

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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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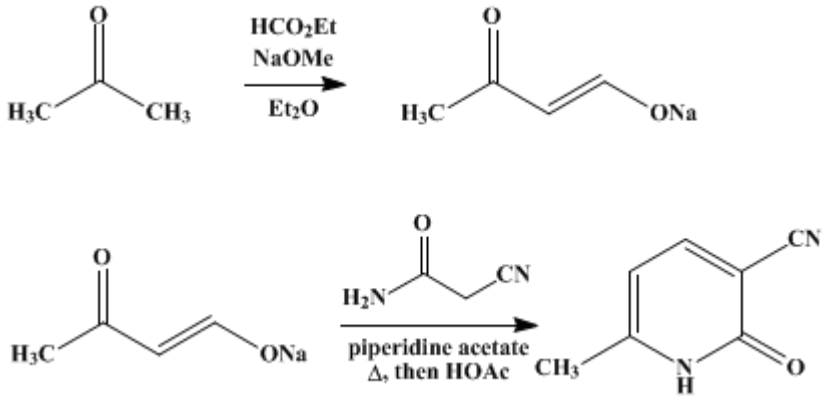
3-CYANO-6-METHYL-2(1)-PYRIDONE

[Nicotinonitrile, 1,2-dihydro-6-methyl-2-oxo-]



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1. Procedure

In a 2-l. three-necked flask fitted with a Hershberg stirrer sealed by a lubricated rubber sleeve, a dropping funnel, and a reflux condenser attached to a calcium chloride drying tube are placed 46.5 g. (0.86 mole) of sodium methoxide (Note 1) and 1 l. of ether (dried over sodium wire). The flask is cooled in an ice bath, and a mixture of 46.4 g. (0.8 mole) of acetone (Note 2) and 59.2 g. (0.8 mole) of ethyl formate (Note 3) is added through the dropping funnel at a rate of about 2 drops per second, with stirring, during a period of about 1 hour. Stirring is continued 15 minutes longer with the ice bath in place and then 1 hour after it is removed. The reflux condenser is replaced by a condenser set for distillation, and the ether is distilled by heating the mixture in a water bath at a temperature which is not allowed to rise above 70°. Stirring is continued as long as possible during the distillation. The last of the ether is removed by distillation under reduced pressure with the aid of a water aspirator (Note 4).

To the solid residue of sodium formylacetone remaining in the flask are added a solution of 67 g. (0.8 mole) of cyanoacetamide (Note 5) in 400 ml. of water and piperidine acetate (prepared by adding piperidine to 8 ml. of glacial acetic acid in 20 ml. of water until the solution is just basic to litmus). The flask is equipped with a reflux condenser, and the mixture is heated under reflux for 2 hours. At the end of this time 200 ml. of water is added, and the solution is acidified (to litmus) with acetic acid, causing separation of the product as a voluminous yellow precipitate. The mixture is cooled in an ice bath for 2 hours, and the product is collected on a suction filter, washed on the filter with three 100-ml. portions of ice water, and dried (Note 6). The yield of 3-cyano-6-methyl-2(1)-pyridone is 59–67 g. (55–62%); m.p. 292–294° (dec., cor.) (Note 7), (Note 8), and (Note 9).

2. Notes

1. Commercial sodium methoxide obtained from the Mathieson Alkali Works was used. If the commercial product is not available, sodium methoxide can be prepared by dissolving clean sodium in dry methanol and removing the excess methanol by distillation and finally by heating the residue to 200° under good vacuum furnished by an oil pump (protected by Dry Ice traps).[2]
2. Reagent grade acetone is dried over potassium carbonate and distilled.
3. Commercial ethyl formate was purified by the procedure described earlier.[3]
4. If not all the ether is removed, it will be impossible to obtain the reflux temperature needed for the subsequent condensation, in which case the remainder of the ether must be removed by a preliminary distillation after adding the aqueous solution of cyanoacetamide and piperidine acetate.
5. Either Eastman Kodak Company white label grade cyanoacetamide or a product prepared according

to the procedure described previously[4] can be used.
6. The product retains water tenaciously and is best dried in a vacuum oven at 70–100° at a pressure of 30 mm. or lower.
7. Melting points determined in the ordinary way are unsatisfactory because gradual decomposition occurs over a broad temperature range. Reproducible melting points were obtained by placing the sample in a melting-point tube and displacing the air in the tube with nitrogen introduced through a fine capillary (prepared by drawing out a piece of glass tubing, which then was attached to a nitrogen cylinder through a T-tube dipping into 1–2 cm. of mercury). The nitrogen-filled melting-point tube was sealed quickly, and the melting point was determined by placing the tube in a bath 10° below the melting point and raising the temperature 2° per minute.
8. Analysis of the crude product is approximately 0.9% low in carbon. Analytically pure 3-cyano-6-methyl-2(1)-pyridone, m.p. 296.5–298.5° (dec., cor., under nitrogen), can be obtained by one recrystallization from 50% (by volume) ethanol, using 66 ml. per g. of product and treating the hot solution with Darco. Recovery of the product is 60%, and concentration of the mother liquor yields impure material.
9. A similar procedure can be used for preparing other 2(1)-pyridones. For example, 3-cyano-6-isobutyl-2(1)-pyridone can be obtained from the sodium salt of formylmethyl isobutyl ketone, and 3-cyano-5,6-dimethyl-2(1)-pyridone can be prepared from the sodium salt of α-formylethyl methyl ketone.[5]

3. Discussion

The procedure used for preparing the sodium salt of formylacetone is a modification of a previously described procedure.[2] 3-cyano-6-methyl-2(1)-pyridone has been prepared by the condensation of β-ethoxycrotonaldehyde diethyl acetal[6] or acetoacetaldehyde bismethylacetal[7] with cyanoacetamide, and by the condensation of the sodium salt of formylacetone with cyanoacetamide.[8]

References and Notes

1. Northwestern University, Evanston, Illinois.
2. Johnson, Woroch, and Mathews, *J. Am. Chem. Soc.*, **69**, 570 (1947).
3. *Org. Syntheses Coll. Vol.* **2**, 180 (1943).
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5. Mariella, *J. Am. Chem. Soc.*, **69**, 2670 (1947).
6. Dornow, *Ber.*, **73B**, 153 (1940).
7. Franke and Kraft, *Chem. Ber.*, **86**, 797 (1953).
8. Perez-Medina, Mariella, and McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).

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

3-Cyano-6-methyl-2(1)-pyridone

sodium formylacetone

3-cyano-6-isobutyl-2(1)-pyridone

sodium salt of formylmethyl isobutyl ketone

3-cyano-5,6-dimethyl-2(1)-pyridone

sodium salt of α-formylethyl methyl ketone

sodium salt of formylacetone

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

acetone (67-64-1)

sodium methoxide (124-41-4)

carbon (7782-42-5)

sodium (13966-32-0)

piperidine (110-89-4)

CYANOACETAMIDE (107-91-5)

ethyl formate (109-94-4)

Nicotinonitrile, 1,2-dihydro-6-methyl-2-oxo- (4241-27-4)

piperidine acetate

β-ethoxycrotonaldehyde diethyl acetal

acetoacetaldehyde bismethylacetal