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](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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

*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.*
ETHYL α-(HEXAHYDROAZEPINYLIDENE-2)ACETATE FROM O-METHYLCAPROLACTIM AND MELDRUM'S ACID

[Acetic acid, (hexahydro-2H-azepin-2-ylidene)-, ethyl ester, (Z)-]


1. Procedure

A. Isopropylidene α-(hexahydroazepinylidene-2)malonate. In a 1-L, round-bottomed flask fitted with an efficient reflux condenser and equipped with a magnetic stirrer are placed 50.8 g (0.40 mol) of O-methylcaprolactim (Note 1), 57.6 g (0.40 mol) of Meldrum's acid (Note 2), and 0.25 g of nickel acetylacetonate monohydrate (Note 3) in 500 mL of anhydrous chloroform. The reaction mixture is refluxed for 12 hr. The solvent is removed with a rotary evaporator and the bright-yellow precipitate is recrystallized from absolute ethanol to give 77–78 g (81–82%) of pale-yellow crystals, mp 147–149°C (Note 4).

B. Ethyl α-(hexahydroazepinylidene-2)acetate. A solution of sodium ethoxide is prepared from 8.3 g (0.36 mol) of freshly cut sodium and 600 mL of freshly distilled absolute ethanol (Note 5) in a 1-L, round-bottomed flask equipped with a magnetic stirrer and fitted with a reflux condenser. To the stirred solution is added in one portion 71.7 g (0.30 mol) of freshly recrystallized isopropylidene α-(hexahydroazepinylidene-2)malonate. The mixture is refluxed and a white precipitate begins to appear. Refluxing is continued for 12 hr. The solvent is removed with a rotary evaporator and the white precipitate is placed in a 2-L beaker. Water (300 mL) is added and a 1 N hydrochloric solution is added dropwise to pH 6. The reaction mixture is extracted with four 100-mL portions of chloroform. The extracts are dried over anhydrous sodium sulfate and the solvent is removed with a rotary evaporator. The yellow solid residue is recrystallized from methanol to give 43–44 g (78–80%) of white powder, mp 55–56°C (Note 6).

2. Notes

1. O-Methylcaprolactim (1-aza-2-methoxy-1-cycloheptene) is available from the Janssen Chimica Society (France) and from the Aldrich Chemical Company, Inc. It may be also prepared from ε-caprolactam and dimethyl sulfate.2

2. Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is available from the Janssen Chimica Society (France) or can be prepared from malonic acid and acetone.3 The checkers purchased Meldrum's acid...
from the Aldrich Chemical Company, Inc.
3. Nickel acetylacetonate monohydrate is a better basic catalyst than triethylamine for the condensation of Meldrum's acid and the lactim ether. The yields are higher and the product is easier to purify.
4. The submitters report mp 145–147°C.
5. Absolute ethanol must be freshly distilled to obtain good yields in the transesterification.
6. The submitters report mp 48–50°C. The product, ethyl α-(hexahydroazepinylidene-2)acetate, shows a Z geometry. The 1H NMR (300 MHz) spectrum of this compound is as follows: δ: 1.22 (t, 3 H, J = 7.1), 1.65 (m, 6 H), 2.25 (m, 2 H), 3.25 (m, 2 H), 4.06 (q, 2 H, J = 7.1), 4.42 (s, 1 H), 8.83 (br s, 1 H).

3. Discussion

This procedure is representative of a general and versatile method for the preparation of cyclic β-enamino esters that are known to be precursors of many alkaloids such as camptothecin, (±)-lamprolobine, (±)-lupinine, or isoretronecanol.

Common synthetic methods for the preparation of cyclic β-enamino esters are the condensation between a lactim ether and benzyl cyanoacetate followed by hydrogenolytic decarboxylation, or the imino ester carbon–carbon condensation with tert-butyl cyanoacetate followed by a trifluoroacetic acid treatment. The use of a thiocarbamid condensated with ethyl bromoacetate gives, after sulfur extrusion by triphenylphosphine, cyclic β-enamino esters. Compared with these methods, the Meldrum's acid condensation followed by the monodecarboxylating transesterification described here is more convenient and practical. An extension of this procedure permits preparation of smaller cyclic β-enamino esters in comparable yields. The results are reported in Table I.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>PREPARATION OF SMALL-RING β-ENAMINO ESTERS</th>
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<tbody>
<tr>
<td>Product</td>
<td>Yield (%)</td>
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<td>B</td>
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Only ethyl or methyl esters can be prepared by this procedure. However, pyrolysis of the cyclic β-enamino diesters at 225°C in the presence of different alcohols, thiols, or amines is a versatile and rapid method for preparing cyclic β-enamino esters, thioesters, or amides.2

References and Notes

Appendix

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

nickel acetylacetonate monohydrate

ethanol (64-17-5)

methanol (67-56-1)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

sulfur (7704-34-9)

dimethyl sulfate (77-78-1)

acetone (67-64-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Malonic acid (141-82-2)

ε-caprolactam (105-60-2)

Ethyl bromoacetate (105-36-2)

hexane (110-54-3)

triethylamine (121-44-8)

trifluoroacetic acid (76-05-1)

O-Methylcaprolactim (2525-16-8)

triphenylphosphine (603-35-0)

2,2-dimethyl-1,3-dioxane-4,6-dione, MELDRUM'S ACID (2033-24-1)
tert-Butyl cyanoacetate (1116-98-9)

1-aza-2-methoxy-1-cycloheptene

benzyl cyanoacetate (14447-18-8)

Ethyl α-(hexahydroazepinylidene-2)acetate

Acetic acid, (hexahydro-2H-azepin-2-ylidene)-, ethyl ester, (Z)- (70912-51-5)

Isopropylidene α-(hexahydroazepinylidene-2)malonate (70912-54-8)