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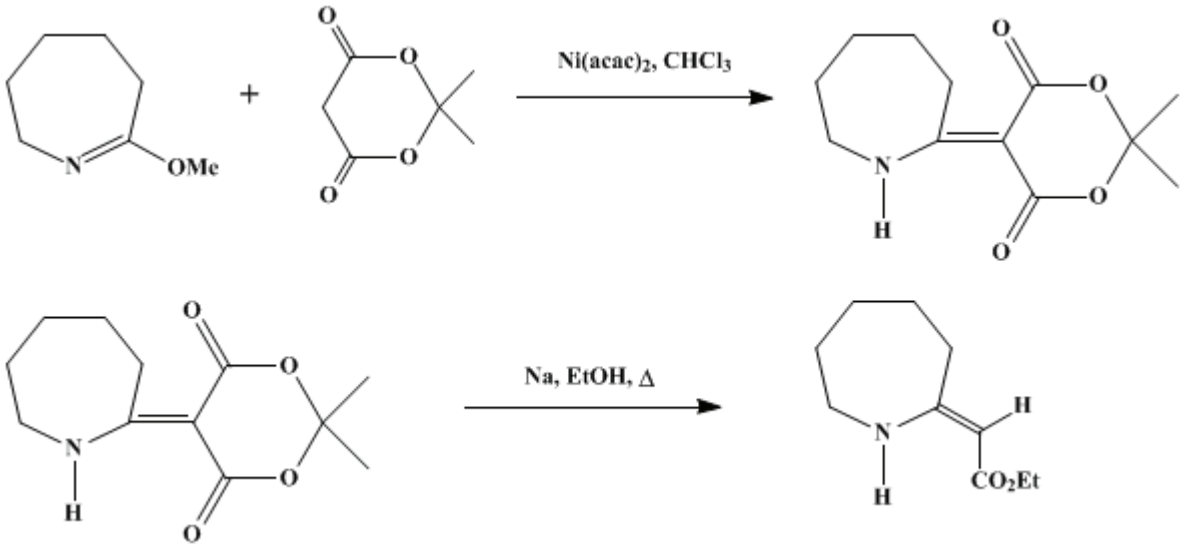
ETHYL α-(HEXAHYDROAZEPINYLIDENE-2)ACETATE FROM *O*-METHYLCAPROLACTIM AND MELDRUM'S ACID

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



Submitted by J. P. Celerier, E. Deloisy-Marchalant, G. Lhommet, and P. Maitte[1].
Checked by Ting-Zhong Wang and Leo A. Paquette.

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

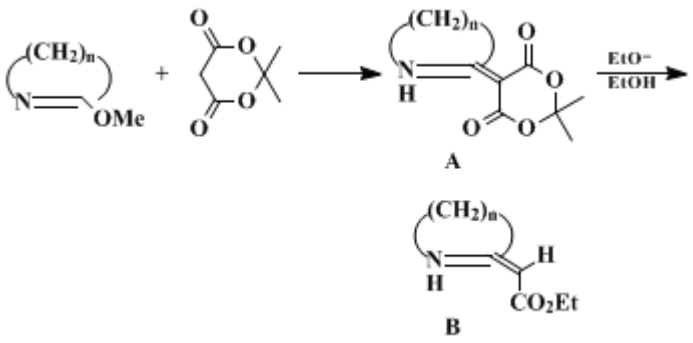
from the Aldrich Chemical Company, Inc.
3. Nickel acetylacetonate monohydrate is a better basic catalyst than triethylamine for the condensation of Meldrum's acid and the lactim ether. The yields are higher and the product is easier to purify.
4. The submitters report mp 145–147°C.
5. Absolute ethanol 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 ^{1}H 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).

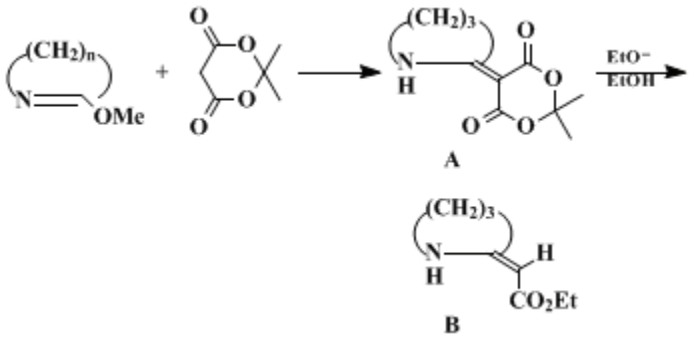
3. Discussion

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,[4] (±)-lamprolobine,[5] (±)-lupinine,[6] or isoretronecanol.[7]

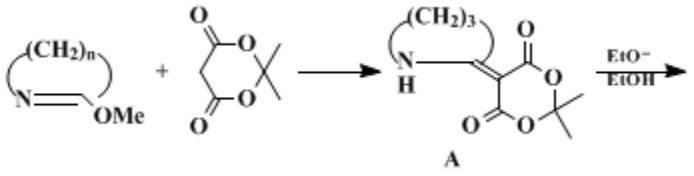
Common synthetic methods for the preparation of cyclic β-enamino esters are the condensation between a lactim ether and benzyl cyanoacetate followed by hydrogenolytic decarboxylation,[8] or the imino ester carbon–carbon condensation with *tert*-butyl cyanoacetate followed by a trifluoroacetic acid treatment.[9] The use of a thiolactam condensed with ethyl bromoacetate gives, after sulfur extrusion by triphenylphosphine,[10] 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.[11] The results are reported in Table I.

TABLE I
PREPARATION OF SMALL-RING β-ENAMINO ESTERS

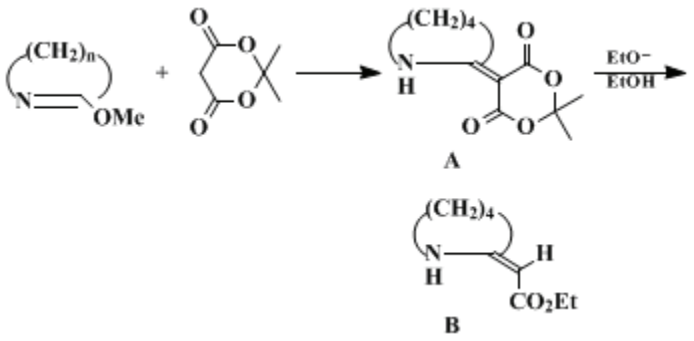


Product	*n*	Yield (%)	mp (solvent) (°C) or bp (mm)	Ref.
	3	92–94	170–172° C (ethanol)	[11]

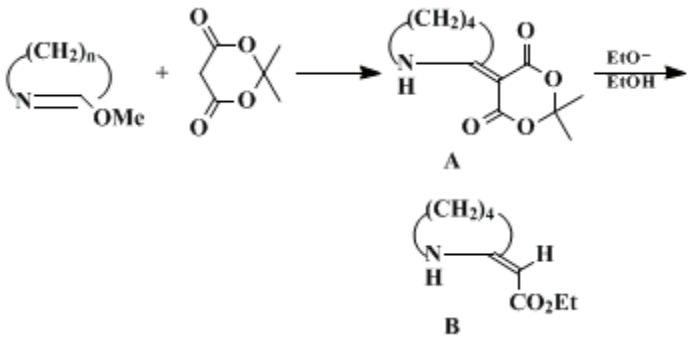
A



B	3	85–87	61–63°C (hexane)	[2,7,11]



A	4	90–92	118–120° C (ethanol)	[11]



B	4	80–84	90–94°C / 0.1 mm	[2,5,6,11]

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

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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)