



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.

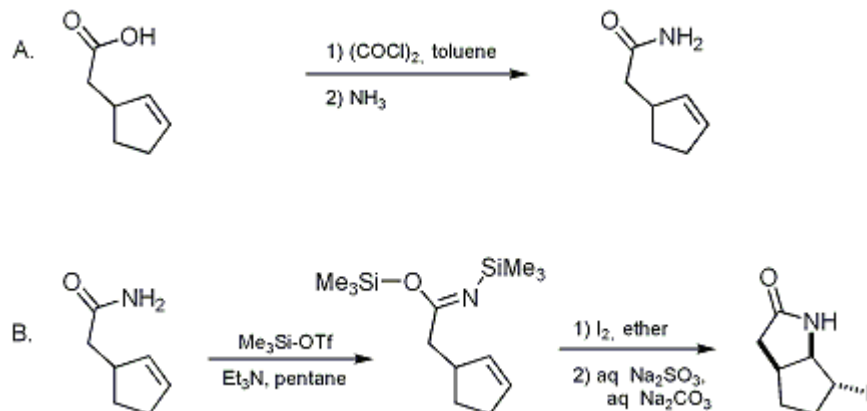
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries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

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 9, p.516 (1998); Vol. 70, p.101 (1992).

IODOLACTAMIZATION: 8-*exo*-IODO-2-AZABICYCLO[3.3.0]OCTAN-3-ONE

[Cyclopenta[b]pyrrol-2(1H)-one, hexahydro-6-iodo-, (3*α*,6*α*,6*α*)-]



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Checked by Chris Melville and James D. White.

1. Procedure

CAUTION! The following operations produce lachrymatory and corrosive vapors and must be carried out in a well-ventilated fume hood.

A. *2-Cyclopentene-1-acetamide*. A dry, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, serum stopper, 25-mL pressure equalizing addition funnel, and an **argon** atmosphere with provision for venting gaseous reaction products (Note 1). The vessel is charged with 20 g (152 mmol) of *2-cyclopentene-1-acetic acid* (Note 2) and 25 mL of dry **toluene** (Note 3). **Oxalyl chloride** (17.3 mL, 1.3 equiv) is added slowly over a 30-min period by means of the addition funnel, taking care to release any pressure buildup. (*Caution: gaseous hydrogen chloride evolution!*.) The dark reaction mixture is stirred for an additional 20 min while the second reaction vessel is assembled, then concentrated to about 2/3 volume at the vacuum pump (Note 4).

A 250-mL, three-necked, round-bottomed flask equipped with magnetic stirring bar, serum stopper, dry ice condenser, and **argon** atmosphere is cooled by means of a dry ice/acetone bath and charged with approximately 150 mL of dry liquid **ammonia**. The *2-(2-cyclopentenyl)acetyl chloride* reaction mixture is added carefully but steadily (Note 5) to the cold and rapidly stirred **ammonia** by syringe. (*Caution: vigorous exothermic reaction!*). Residual acid chloride is transferred by rinsing the first vessel with 5 mL of **toluene**. After the addition the mixture is stirred for an additional 5 min, then 60 mL of **dichloromethane** is added. The cold bath is removed and the excess **ammonia** is allowed to escape into the fume hood by stirring the open vessel overnight.

The crude reaction mixture is filtered and the filtrate is reserved. The solids are triturated by stirring vigorously with 100 mL of **methanol** for 20 min with gentle warming to about 40°C. The solids are filtered and triturated again in the same way. The three organic filtrates are combined and concentrated to near dryness. The resulting semi-solid is redissolved in 100 mL of **dichloromethane**, filtered to remove residual **ammonium chloride**, and concentrated to a light brown solid, 18.9 g. The crude product is dissolved in 60 mL of boiling **tetrahydrofuran** and allowed to crystallize in a -6°C freezer overnight. The amide is collected by filtration, washed with 5 mL of cold **ether**, and dried under reduced pressure, giving 15.77 g of white flakes, mp 128–129°C. The filtrate is concentrated to about 8 mL, brought to the cloud point by the addition of a few drops of **hexane**, and cooled in the freezer. Filtration as before gives

a second crop of white flakes, 1.46 g, mp 128–129°C (total yield 17.23 g, 90.6%) (Note 6).

B. *8-exo-Iodo-2-azabicyclo[3.3.0]octan-3-one*. A dry, 500-mL, three-necked, round-bottomed flask equipped with magnetic stirring bar, serum stopper, 50-mL pressure-equalizing addition funnel, cold water bath, and argon atmosphere is charged with 12.5 g (100 mmol) of 2-cyclopentene-1-acetamide, 29.2 mL (210 mmol) of triethylamine (Note 7), and 80 mL of dry pentane (Note 8). By means of the addition funnel, 41 mL (210 mmol) of trimethylsilyl trifluoromethanesulfonate (Note 9) is slowly added to the cooled and rapidly stirred amide suspension over a 50-min period. After the addition is complete, the reaction mixture is stirred for an additional 20 min at room temperature, then the stirring is stopped, and the two layers are allowed to separate.

A second, dry, 500-mL, three-necked, round-bottomed flask is equipped with magnetic stirring bar, serum stopper, vacuum pump connection, and argon atmosphere. The (top) pentane layer from the first flask, which contains the bis(trimethylsilyl)imidate, is carefully transferred to the second flask by cannula, maintaining the argon atmosphere, and leaving the oily triethylammonium trifluoromethanesulfonate layer behind. This remaining salt is triturated with 30 mL of a dry 2:1 pentane/ether mixture by stirring for 15 min, allowing the layers to separate, then transferring the extract to the second flask as before. The trituration is repeated with a 30-mL portion of anhydrous ether, and the combined extracts in the second flask are concentrated with stirring to about 1/3 volume using the vacuum pump (Note 10).

A third, dry, 500-mL, three-necked, round-bottomed flask equipped with an addition funnel, magnetic stirring bar, serum stopper, cold water bath, and argon atmosphere is charged with 53.3 g (210 mmol) of molecular iodine and 140 mL of anhydrous ether. The mixture is allowed to stir for 10 min to dissolve most of the iodine. The concentrated organic extract in the second flask is now added to the iodine solution with stirring and cooling over 15 min. The reaction mixture warms slightly during the addition, but should not reach reflux. An additional 10 mL of anhydrous ether is used to complete the transfer of the bis(trimethylsilyl)imidate. Near the end of the addition, the oily black layer (which contains the cyclized iminium salt) solidifies, leaving a clear light brown ether supernatant. The serum stopper is carefully removed and the solid residue gently broken up using a spatula. The stopper is replaced and the reaction mixture is allowed to stand for an additional 45 min with occasional swirling by hand. The reaction is quenched by removing the addition funnel and stopper and slowly adding 20 mL of saturated aqueous sodium carbonate. (*Caution: vigorous gas evolution!*). At this point stirring can be resumed. A 20-mL portion of saturated aqueous sodium sulfite is added slowly (*more gas evolution*), and the process is repeated until 100 mL each of saturated aqueous sodium carbonate and sulfite have been added. The reaction mixture is filtered, the crude solid iodolactam is reserved, and the organic layer is separated and reserved. The aqueous layer is saturated with sodium chloride and extracted with four, 100-mL portions of dichloromethane. The five organic extracts are combined, dried over anhydrous sodium sulfate, and concentrated to a light brown solid. This residue is dissolved in 20 mL of tetrahydrofuran and hexane is added to the cloud point. Cooling in the freezer gives colorless needles, which are collected and dried under reduced pressure to afford 1.60 g of iodolactam, mp 138–139°C.

The reserved solid from filtration is dried under reduced pressure, dissolved in 65 mL of hot tetrahydrofuran and filtered. The solution is allowed to cool, first at room temperature, then in the freezer. The product (16.77 g, mp 138–139°C) is collected as before. The mother liquor is concentrated to about 10 mL, brought to the cloud point by the addition of hexane, and cooled in the freezer, resulting in an additional crop of 1.70 g, mp 138–139°C. The total amount of iodolactam is 19.80 g, representing a 79% yield from the amide (Note 11).

2. Notes

1. All reaction glassware was oven dried at 120°C and assembled hot. The submitters used three evacuate/fill cycles from an argon-filled balloon fitted on a three-way stopcock to provide the inert atmosphere.
2. 2-Cyclopentene-1-acetic acid (96%) was purchased from Aldrich Chemical Company, Inc., and used as received.
3. Toluene was dried by distillation from –40 mesh calcium hydride. Unless otherwise specified,

reagents in this procedure were obtained commercially and used as received.

4. In series with the usual (500 mL) dry ice/acetone trap, a trap filled with solid [sodium hydroxide](#) was used to protect the pump from acidic vapors.

5. Continuous addition of the carboxylic acid chloride solution is required to prevent clogging the syringe needle.

6. The spectral properties are as follows: FT-IR (KBr) cm^{-1} : 3360, 3355, 1663, 1634; ^1H NMR (400 MHz, CDCl_3) δ : 1.42–1.49 (m, 1 H), 2.07–2.35 (m, 5 H), 3.06–3.09 (m, 1 H), 5.66 (br s, 1 H), 5.75 (app dd, 1 H, $J = 2, 5$), 5.76 (app dd, 1 H, $J = 2.5, 4.5$), 5.94 (br s, 1 H); ^{13}C NMR δ : 29.6, 31.8, 42.0, 42.3, 131.7, 133.7, 175.0.

7. [Triethylamine](#) was dried by distillation from -40 mesh [calcium hydride](#).

8. [Pentane](#) was dried by distillation from -40 mesh [calcium hydride](#).

9. [Trimethylsilyl trifluoromethanesulfonate](#) (99%) was purchased from Aldrich Chemical Company, Inc., and used as received.

10. Any adventitious water introduced during these operations results in a decreased yield of iodo lactam and the formation of iodo lactone as an undesired side product.

11. The spectral properties are as follows: FT-IR (KBr) cm^{-1} : 3189, 3078, 3034, 1680; ^1H NMR (400 MHz, CDCl_3) δ : 1.55–1.60 (m, 1 H), 1.99–2.06 (m, 1 H), 2.10–2.20 (m, 2 H), 2.33–2.45 (m, 1 H), 2.70 (dd, 1 H, $J = 18, 10$), 3.05–3.13 (m, 1 H), 4.16 (br s, 1 H), 4.40 (d, 1 H, $J = 7.2$), 5.75–5.85 (br s, 1 H); ^{13}C NMR δ : 32.3, 32.9, 35.0, 35.5, 38.2, 69.8, 178.6.

Waste Disposal Information

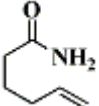
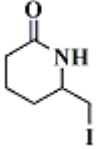
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

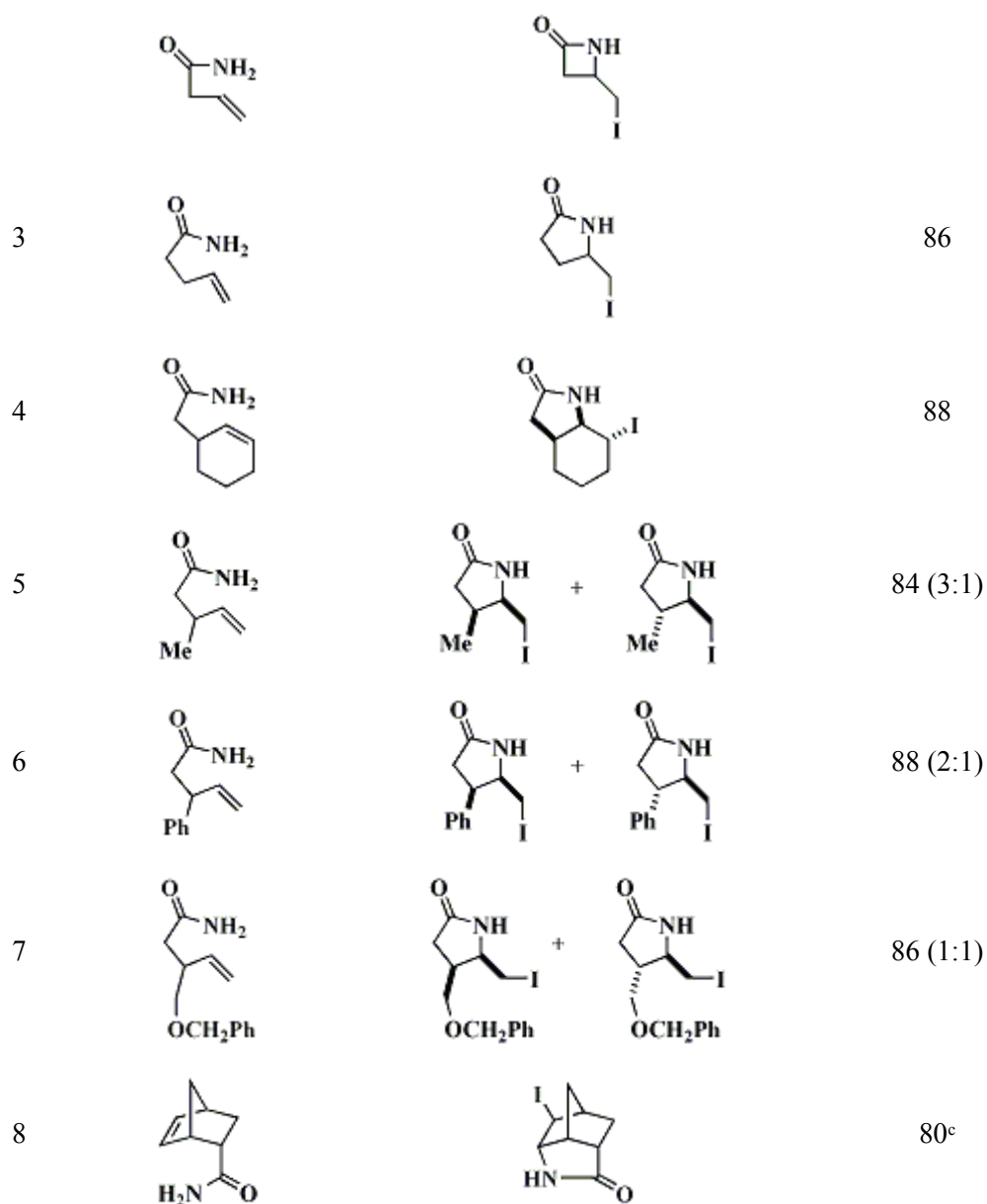
3. Discussion

This "iodolactamization" procedure has been optimized for the present example. Related reaction conditions have been used to generate a series of iodo lactams from the corresponding unsaturated amides (Table).^{2,3} For these (smaller scale) examples, the cyclization was carried out in [tetrahydrofuran](#) solution, and isolation was by column chromatography. The lactams in entries 3, 4, and 8 have also been prepared by the submitters in 81%, 82%, and 78% yields, respectively, using the procedure described herein. Cyclization in [ether](#) solution rather than in [tetrahydrofuran](#) avoids the formation of [iodobutanol](#),³ which must then be separated from product.

Iodo lactams are a useful, new class of difunctional compounds.² Conversions of iodo lactams to N-acylaziridines,^{3,4} unsaturated lactams,^{3,5} azido lactams,^{3,4} amino lactams,^{3,4} hydroxy lactams,³ seleno lactams,^{6,7} annulated lactams,^{3,6,7,8} and other derivatives² have been described. Syntheses of ezoaminuroic acid⁵ and slaframine^{6,7} have used halo lactamizations for key steps. Halo lactams have also been prepared from [aspartic acid](#)⁸ and [glutamic acid](#),⁹ from N-substituted unsaturated amides^{10,11,12,13,14} and imidates,^{15,16,17} and from unsaturated amides whose competing O-cyclization reaction is less favored.^{18,19,20}

TABLE
PREPARATION OF IODO LACTAMS

Entry	Unsaturated Amide	Iodo Lactam(s)	% Yield (cis/trans)
1			35 ^a
2			35 ^b



^a10–20% of starting amide was also recovered. ^b54% of crotonamide was also isolated. ^cOverall yield after separate desilylation.

References and Notes

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

sodium carbonate and sulfite

ezoaminuroic acid

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

iodine (7553-56-2)

toluene (108-88-3)

Glutamic Acid (56-86-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

hexane (110-54-3)

aspartic acid (56-84-8)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

iodo

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

8-exo-Iodo-2-azabicyclo[3.3.0]octan-3-one (100556-58-9)

2-Cyclopentene-1-acetamide (72845-09-1)

2-cyclopentene-1-acetic acid

2-(2-Cyclopentenyl)acetyl chloride

iodobutanol

crotonamide (23350-58-5)

Cyclopenta[b]pyrrol-2(1H)-one, hexahydro-6-iodo-, (3 α ,6 α ,6 α)-