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.

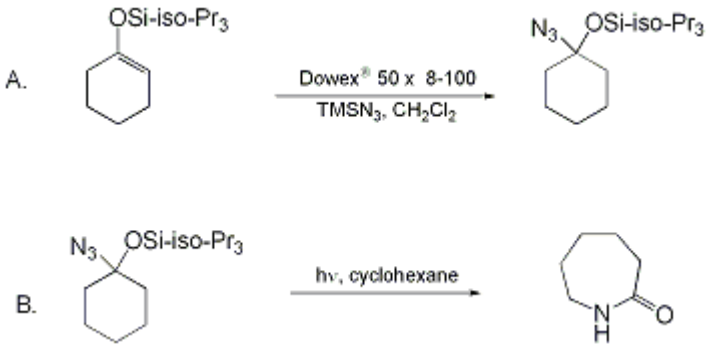
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.079.0165

Organic Syntheses, Coll. Vol. 10, p.207 (2004); Vol. 79, p.165 (2002).

PHOTO-INDUCED RING EXPANSION OF 1-TRIISOPROPYLSILYLOXY-1-AZIDOCYCLOHEXANE: PREPARATION OF ε-CAPROLACTAM

[2*H*-Azepin-2-one, hexahydro- from Silane, [(1-azidocyclohexyl)oxy]tris(1-methylethyl)-]



Submitted by Jade D. Nelson, Dilip P. Modi, and P. Andrew Evans[1] .
Checked by Patrick Foyle, Peter Belica, and Steven Wolff.

1. Procedure

A. *1-Triisopropylsilyloxy-1-azidocyclohexane* : A 2-L, two-necked, round-bottomed flask is equipped with a magnetic stirrer, argon inlet, and a rubber septum (Note 1). The flask is charged with freshly-distilled 1-triisopropylsilyloxycyclohexene (25.47 g, 100 mmol, Note 2) and anhydrous dichloromethane (1.0 L, Note 3). Azidotrimethylsilane (68.5 mL, 500 mmol, Note 4) is added via syringe, immediately followed by anhydrous Dowex® 50 × 8-100 (24.98 g, Note 5) in a single portion from a dry flask. The suspension is stirred vigorously at ambient temperature for ca. 48 hr (Note 6). The reaction mixture is filtered to recover the Dowex® resin and solvent is removed under reduced pressure to afford a clear, colorless oil. The crude oil is applied to a 5 × 13-cm column of silica gel (120 g, 230-400 mesh packed with hexanes). The column is quickly eluted with hexanes (750 mL) and fractions are collected in 25-mL test tubes (Note 7). The fractions containing the desired product are identified by thin layer chromatography, combined, and concentrated under reduced pressure to afford the 1-triisopropylsilyloxy-1-azidocyclohexane (26.75 g, 90%) as a colorless oil (Note 8).

B. *ε-Caprolactam* : The reaction apparatus (see Fig. 1, Note 9) is charged with 1-triisopropylsilyloxy-1-azidocyclohexane (25.9 g, 87.1 mmol) and cyclohexane (435 mL, Note 10). The clear, colorless solution is purged with nitrogen for a 15 min period to exclude oxygen. The solution is cooled to ca. 0°C and irradiated (≥200 nm) for 3.5 hr (Note 11). The solvent is removed under reduced pressure to afford a pale yellow oil. The crude oil is dissolved in dichloromethane (ca. 10 mL) and applied to a 6 × 6-cm column of silica gel (88 g, 230-400 mesh packed with 1 : 1 ethyl acetate/hexanes). An additional 1 cm of silica gel is added to the top of the column and the mixture is stirred with a glass rod to homogenize the layer, rinsed with eluent, and the column is repacked. The column is eluted with 1 : 1 ethyl acetate/hexanes (200 mL, Note 12), then with 1 : 9 methanol/ethyl acetate (500 mL), and fractions are collected in 25-mL test tubes. The fractions containing the desired product are identified by thin layer chromatography (Note 13), combined, and concentrated under reduced pressure to afford *ε-caprolactam* (8.20 g, 83%, Note 14) as an off-white solid.

2. Notes

1. The assembled glassware was flame-dried under high vacuum, then cooled to ambient temperature under a positive pressure of dry argon.

2. The following procedure was used to prepare 1-triisopropylsilyloxycyclohexene . A 500-mL, three-necked, round-bottomed flask was charged with 9.81 g (0.10 mol) of cyclohexanone , 180 mL of dry dichloromethane (anhydrous grade from Aldrich Chemical Company, Inc.), and 20.9 mL (0.15 mol) of triethylamine . The mixture was cooled to −20° and a solution of 32.25 mL of triisopropylsilyl trifluoromethanesulfonate [2] in 20 mL of dichloromethane was added dropwise, while maintaining the temperature of the reaction below 5°C. After completion of the addition, the reaction mixture was stirred at 0-5°C for 1 hr, then at ambient temperature for 2 hr. The reaction mixture was washed with 80 mL of brine, then dried with magnesium sulfate . After filtration to remove the drying agent, the filtrate was concentrated under vacuum to yield a residue consisting of two phases. The residue was diluted with 200 mL of hexanes, washed with 50 mL of brine, dried with magnesium sulfate , and filtered. The filtrate was concentrated under vacuum to give 28.37 g of a pale yellow oil. Distillation afforded 24.97 g of a colorless oil, bp 75-85°C (0.2-0.3 torr, 0.15-0.23 mm). The NMR spectrum of this material indicated the possible presence of cyclohexanone . Redistillation gave 20.25 g (78%) of 1-triisopropylsilyloxycyclohexene as a colorless oil, bp 85-90°C (0.3 torr, 0.23 mm).
3. Dichloromethane was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use.
4. The azidotrimethylsilane was purchased from Acros Organics and used without further purification.
5. Dowex® 50X8-100 was purchased from Acros Organics and dried in the following manner. Approximately 50 g of the commercially available resin is washed with anhydrous methanol (3 × 50 mL), then with anhydrous ethyl ether (2 × 50 mL) in a Buchner funnel. The granular solid is dried under high vacuum for *ca.* 24 hr.
6. The progress of the reaction is monitored by thin layer chromatography, eluting with hexanes, then dried quickly with a stream of nitrogen and eluted a second time with hexanes (product R_f = 0.75, visualized and developed using UV light and $KMnO_4$, respectively). The checkers found that the reaction was not complete after 72 hr. Stirring was continued until TLC analysis indicated the absence of the enol ether (5-6 days).
7. Discoloration of the column is often observed, which may be due to hydrazoic acid formation upon hydrolysis of the azidotrimethylsilane .
8. The product exhibits the following spectroscopic and analytical properties: IR (neat) cm^{-1}: 2948, 2892, 2865, 2104 ; ^1H NMR (250 MHz, C_6D_6) δ: 1.04-1.18 (m, 21 H), 1.26-1.57 (m, 8 H), 1.66-1.76 (m, 2 H) ; ^{13}C NMR (62.5 MHz, C_6D_6) δ: 13.56, 18.45, 23.4, 25.16, 38.50, 91.57 ; HRMS (EI) calcd for $C_{11}H_{24}N_3OSi$ 254.1689 found 254.1674 . Anal. calcd. for $C_{15}H_{31}N_3OSi$: C, 60.56; H, 10.50; N, 14.12 Found: C, 60.51; H, 10.76; N, 14.04.
9. The reaction apparatus (Figure 1) requires a tubular quartz flask with two side arms and a large ground-glass joint at the top to accommodate the water-cooled UV lamp. One of the side arms is fitted with a Teflon® tube, the second side arm is fitted with a rubber septum and wide-bore needle, which has a Teflon® tube leading to a nitrogen bubbler. A vigorous stream of nitrogen is allowed to flow into the flask through the Teflon® tube to agitate the solution during irradiation. The entire apparatus is placed inside a vacuum-jacketed Dewar flask filled with ice to maintain the reaction temperature at *ca.* 0°C.
10. Cyclohexane was purchased from Acros Organics and used without further purification.
11. The UV lamp generates a great deal of heat, and thus it is necessary to interrupt the reaction *ca.* every hour to remove water from the Dewar and replenish it with ice.
12. The triisopropylsilanol side-product is eluted first through the column. Alternatively, the bulk of this material may be removed via distillation under reduced pressure (50-60°C at 2-3 mmg).
13. The progress of the reaction is monitored by thin layer chromatography, eluting with ethyl acetate (product R_f = 0.06, visualized and developed using UV light and $KMnO_4$, respectively).
14. The product exhibits the following spectroscopic and analytical properties: mp 68-69°C; lit.[3] 68-70° C; IR ($CHCl_3$) cm^{-1}: 3420, 3293, 3224, 3019, 2937, 2859, 1660 ; ^1H NMR (250 MHz, C_6D_6) δ: 1.14-1.33 (m, 6 H), 2.21-2.25 (m, 2 H), 2.68-2.74 (m, 2 H), 8.33 (bs, 1 H) ; HRMS (EI) calcd for $C_6H_{11}NO$: 113.0841; found: 113.0833 .

Waste Disposal Information

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

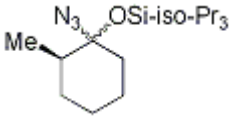
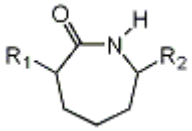
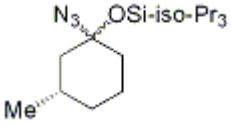
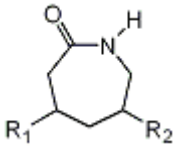
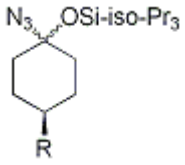
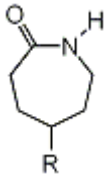
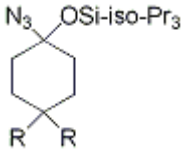
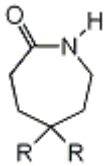
3. Discussion

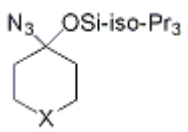
The synthesis of lactams has attracted considerable attention in recent years. This is presumably because they represent versatile synthetic intermediates that are present in many biologically important molecules.[4] Despite the wide range of methodologies that have been examined for the synthesis of lactams,[5] [6] the Beckmann[7] and Schmidt[8] rearrangements still remain by far the most convenient and general methods. The strongly acidic conditions required for the Schmidt rearrangement often lead to undesired by-products. This is a major limitation particularly with acid-labile substrates.

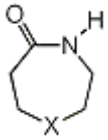
The method outlined here[9] represents a convenient and environmentally benign Schmidt rearrangement, in which the azidohydrin is prepared using a recyclable acid catalyst and trimethylsilyl azide , a non-explosive source of azide.[10] Photolysis of the azidocyclohexane results in the ring expansion, probably through the formation of a reactive nitrene. The by-products from this reaction are gases or innocuous silanes. The main limitation with the method is that at present the ring expansion is not regioselective, as exemplified by entries 1 and 2 in the Table, in which a mixture of regioisomers is obtained.

A further advantage of this protocol is that it allows the azidohydrin intermediate to be isolated. This will facilitate important mechanistic work to clarify the nature of the reactive species responsible for the ring expansion. Although only the preparation of azepin-2-ones have been reported, other ring sizes have also been successfully examined. Hence, this method provides a general method for the preparation of lactams.

TABLE[9]
PREPARATION OF AZEPIN-2-ONES VIA THE PHOTO-INDUCED RING EXPANSION OF AZIDOCYCLOHEXANES

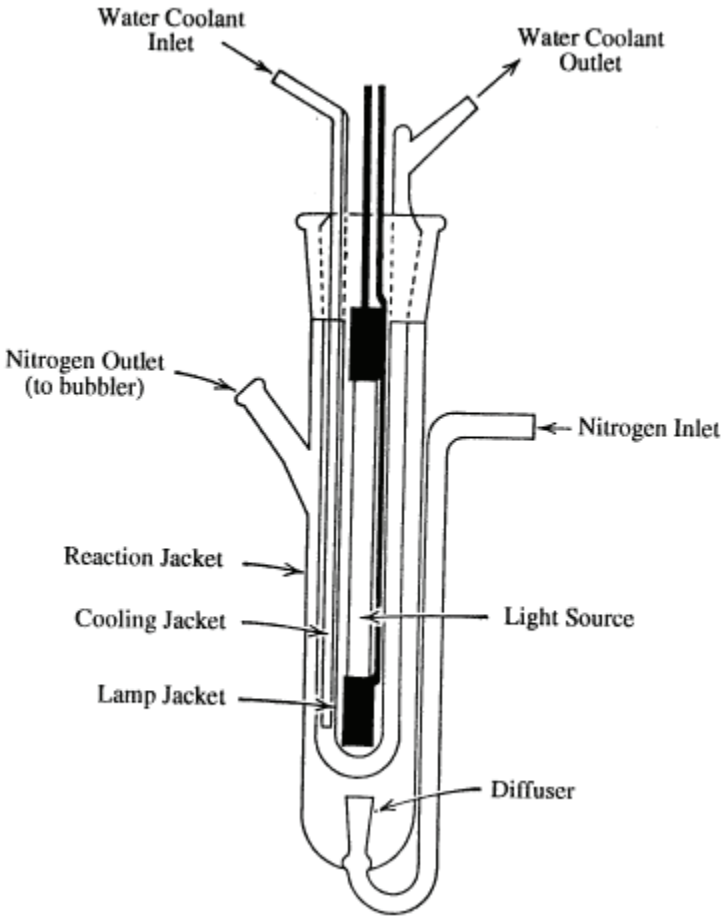
Entry	α-Azidohydrin[a]	Azepin-2-ones		Yield (%)[b]
1			R_1= Me; R_2 = H R_1= H; R_2 = Me	75 [c]
2			R_1= Me; R_2 = H R_1= H; R_2 = Me	87 [d]
3			R = Me R =*tert*-Bu	89 85
4			R = R = Me R=R= $O(CH_2)_2O$	85 82
5			X = O X = S	83 64





[a]Photolysis with ultraviolet light at 0°C on a 0.25-mmol reaction scale for *ca.* 1 hr.
[b]Isolated yields.
[c]1.6 : 1 Mixture regioisomers.
[d]1 : 1 Mixture of regioisomers.

Figure 1



References and Notes

1. Brown Laboratory, Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716. Present address: Department of Chemistry, Indiana University, Bloomington, IN 47405.
2. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D.H. *Tetrahedron Lett.* **1981**, *22*, 3455.
3. Marvel, C. S.; Eck, J. C. *Org. Synth.*, *Coll. Vol. II* **1943**, 371.
4. Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131.
5. (a) Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron: Asymmetry* **1990**, *1*, 593; (b) Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron Lett.* **1992**, *33*, 6857; (c) Evans, P. A.; Holmes, A. B.; Russell, K. *J. Chem. Soc., Perkin Trans. I* **1994**, 3397; (d) Evans, P. A.; Holmes, A. B.; McGeary, R. P.; Nadin, A.; Russell, K.; O'Hanlon, P. J.; Pearson, N. D. *J. Chem. Soc. Perkin*

Trans. I **1996**, 123.

6. (a) Kawase, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1076; (b) Vedejs, E.; Sano, H. *Tetrahedron Lett.* **1992**, *33*, 3261; (c) Kim, S.; Joe, G. - H.; Do, J. - Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328; (d) McGee, D. I.; Ramaseshan, M. *Synlett*, **1994**, 743; (e) Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* **1994**, 949; (f) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; Dimarco, J. D. *J. Am. Chem. Soc.*, **1994**, *116*, 2348; (g) Coates, B.; Montgomery, D.; Stevenson, P. J. *Tetrahedron* **1994**, *50*, 4025; (h) Nadin, A.; Derrer, S.; McGeary, R. P.; Goodman, J. M.; Raithby, P. R.; Holmes, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 9768. (i) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449. (j) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaria, J.; Suárez-Sobrino, A. *J. Org. Chem.* **1997**, *62*, 9229. (k) Benati, L.; Nanni, D.; Sangiorgi, C.; Spagnolo, P. *J. Org. Chem.* **1999**, *64*, 7836. (l) Bottcher, G.; Reissig, H.- U. *Synlett* **2000**, 725 and pertinent references cited therein.
7. (a) Schmidt, K. F. *Z. Angew. Chem.* **1923**, *36*, 511; (b) Wolff, H. *Org. React.* **1946**, *3*, 307.
8. Beckmann, E. *Chem. Ber.* **1886**, *19*, 988.
9. Evans, P. A.; Modi, D. P. *J. Org. Chem.* **1995**, *60*, 6662.
10. Trimethylsilyl azide has been reported to be a non-explosive alternative to hydrazoic acid: Birkofer, L.; Wegner, P. *Org. Synth.*, *Coll. Vol. VI* **1988**, 1030.

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

1-Triisopropylsilyloxy-1-azidocyclohexane:
Silane, [(1-azidocyclohexyl)oxy]tris(1-methylethyl)- (13); (172090-42-5)

1-Triisopropylsilyloxycyclohexene:
Silane, (1-cyclohexen-1-yloxy)tris(1-methylethyl)- (11); (80522-46-9)

ε-Caprolactam:
2H-Azepin-2-one, hexahydro- (8, 9); (105-60-2)

Azidotrimethylsilane: HIGHLY TOXIC:
Silane, azidotrimethyl- (8, 9); (4648-54-8)

Cyclohexanone (8, 9); (108-94-1)

Triethylamine (8);
Ethanamine, N, N-diethyl- (9); (121-44-8)

Triisopropylsilyl trifluoromethanesulfonate:
Methanesulfonic acid, trifluoro-, tris(1-methylethyl)silyl ester (11); (80522-42-5)