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.

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.

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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.

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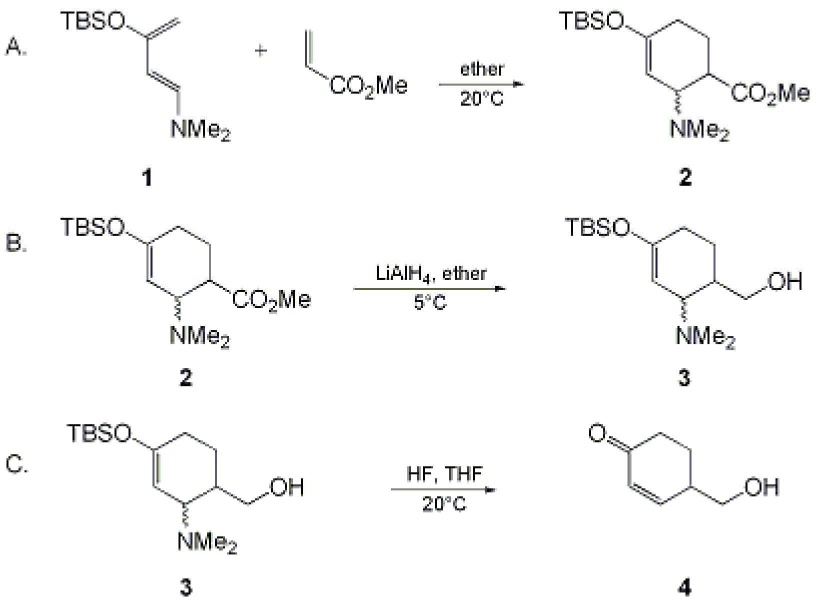
[4+2] CYCLOADDITION OF 1-DIMETHYLAMINO-3-tert-BUTYLDIMETHYLSILOXY-1,3-BUTADIENE WITH METHYL ACRYLATE: 4-HYDROXYMETHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 4-(hydroxymethyl)-]



Submitted by Sergey A. Kozmin, Shuwen He, and Viresh H. Rawal[1] .
Checked by Ruth Figueroa and David J. Hart.

1. Procedure

A. 4-Carbomethoxy-3-dimethylamino-1-tert-butyldimethylsiloxy-1-cyclohexene , **2**. A dry, 250-mL, round-bottomed flask is charged with 1-dimethylamino-3-tert-butyldimethylsiloxy-1,3-butadiene (16.6 g, 0.073 mol) and anhydrous ether (30 mL) (Note 1). Methyl acrylate (13.5 mL, 0.15 mol) (Note 2)is added in one portion and the resulting light yellow solution is allowed to stand for 20 hr at room temperature. The solution is concentrated on a rotary evaporator, and the residual methyl acrylate is removed under high vacuum to afford 22.4 g (98%) of the desired cycloadduct **2**, in good purity, as a pale-yellow oil (Note 3).

B. 4-Hydroxymethyl-3-dimethylamino-1-tert-butyldimethylsiloxy-1-cyclohexene , **3**. A dry, 500-mL, three-necked, round-bottomed flask is equipped with a 150-mL pressure-equalizing addition funnel, a reflux condenser topped with an inert atmosphere line, a glass stopper, and an egg-shaped magnetic stirring bar. The flask is charged with lithium aluminum hydride (2.66 g, 0.070 mol) and anhydrous ether (50 mL) (Note 1). The flask is cooled to 5°C in an ice-water bath. A solution of cycloadduct **2** (22.4 g, 0.072 mol) in ether (80 mL) is transferred to the addition funnel and added over a 30-min period. The reaction mixture is stirred for another 15 min, diluted with ether (100 mL), and quenched by dropwise addition of water (9 mL). The ice-water bath is removed, the resulting gray suspension is allowed to reach room temperature, and the mixture is stirred vigorously for an additional 60 min. The mixture is transferred to a 1.0-L Erlenmeyer flask and diluted with 350 mL of ether. Anhydrous sodium sulfate (Na_2SO_4) (60 g) is added, the suspension is stirred for 30 min, and filtered. The filter cake is washed twice with ether (50 mL each time). The solvent is removed on a rotary evaporator and the remaining volatile material is removed under high vacuum to afford 18.6 g (91%) of the desired amino alcohol **3** as a viscous clear oil (Note 4).

C. 4-Hydroxymethyl-2-cyclohexen-1-one , **4**. (*Caution: Hydrofluoric acid (HF) is extremely toxic!*)

A 500-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with amino alcohol **3** (16.0 g, 0.056 mol) and tetrahydrofuran (THF) (300 mL). The flask is cooled to 5°C in an ice-water bath. A 4.0 M solution of HF in THF (32 mL, 0.128 mol) (Note 5) is added over 15 min to the cold solution of the amino alcohol. The reaction mixture is stirred at room temperature for 20 hr. THF is removed on a rotary evaporator, maintaining the bath temperature below 40°C. Ethyl acetate (250 mL) is added, and the organic layer is washed with 1.2 M aqueous hydrochloric acid (HCl) solution (40 mL). The aqueous layer is reextracted with ethyl acetate (5 × 100 mL each). Solid sodium bicarbonate ($NaHCO_3$) (15 g) is added to the combined organic layers, followed by stirring for 1 hr and subsequent addition of anhydrous magnesium sulfate ($MgSO_4$). The solution is filtered and solvent is removed on a rotary evaporator to afford the crude enone, which is further purified by bulb-to-bulb distillation (0.2 mm, oven temperature 140-180°C, Note 6) to give 5.90 g (84%) of 4-hydroxymethyl-2-cyclohexen-1-one (Note 7) as a viscous pale-yellow oil.

2. Notes

1. Anhydrous ether was purchased from Fisher Scientific Company and was not further purified.
2. Methyl acrylate was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
3. The cycloadduct consists of a 1.5:1.0 mixture of trans- and cis-diastereomers: ^{1}H NMR of cis-diastereomer (300 MHz, $CDCl_3$) δ: 0.16 (s, 6 H), 0.93 (s, 9 H), 1.83 (m, 1 H), 2.0-2.2 (m, 3 H), 2.27 (s, 6 H), 2.62 (m, 1 H), 3.56 (dd, 1 H, J = 5.0, 5.0), 3.70 (s, 3 H), 4.95 (d, 1 H, J = 5.0) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.4, 18.0, 20.9, 25.6, 28.9, 43.5, 44.8, 51.3, 59.2 100.7, 153.7, 174.6 ; ^{1}H NMR of trans-diastereomer (300 MHz, $CDCl_3$) δ: 0.14 (s, 3 H), 0.15 (s, 3 H), 0.92 (s, 9 H), 1.7-2.0 (m, 2 H), 2.0-2.2 (m, 2 H), 2.24 (s, 6 H), 2.52 (ddd, 1 H, J = 12.7, 9.2, 3.8), 3.66 (m, 1 H), 3.70 (s, 3 H), 4.84 (dd, 1 H, J = 2.0, 1.8) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5, −4.3, 18.0, 25.5, 25.6, 29.0, 40.6, 42.3, 51.7, 61.9, 102.6, 152.4, 176.0 .
4. This material is a mixture of diastereomers. Selected peaks from each diastereomer follow: ^{1}H NMR of major diastereomer (400 MHz, C_6D_6) δ: 0.98 (s, 9 H, CMe_3), 1.99 (s, 6 H, NMe_2), 4.81 (broad s, 1 H, =CH) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.4, 18.0, 20.9, 25.6, 28.9, 43.5, 44.8, 51.3, 59.2, 100.7, 153.7, 174.6 ; ^{1}H NMR of minor diastereomer (400 MHz, $CDCl_3$) δ: 1.01 (s, 9 H, CMe_3), 2.05 (s, 6 H, NMe_2), 4.99 (d, 1 H, J = 4, =CH) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.0, −3.8, 18.5, 25.2, 30.1, 39.5, 44.4, 62.0, 44.2, 100.4, 155.0 (one peak not observed).
5. A 4.0 M solution of HF in THF was prepared in a 50-mL plastic bottle by the addition of 4.1 mL of the 49% aqueous HF solution (using a disposable plastic syringe) to THF (28 mL).
6. In order to minimize bumping, a 250-mL, round-bottomed flask was used for the distillation.
7. The checkers obtained 5.72 g (81%) of the enone. This compound displays the following spectral data: IR (neat) cm^{-1}: 3420, 1675 ; ^{1}H NMR (300 MHz, $CDCl_3$)δ: 1.60 (m, 1 H, OH), 1.82 (dddd, 1 H, J = 12.6, 12.6, 9.8, 5.0), 2.14 (dddd, 1 H, J = 12.6, 9.7, 5.0, 1.3), 2.42 (ddd, 1 H, J = 16.8, 12.6, 5.0), 2.56 (ddd, 1 H, J = 16.8, 5.0, 5.0), 2.65 (m, 1 H), 3.71 (m, 2 H), 6.08 (dd, 1 H, J = 10.0, 2.2), 6.96 (ddd, 1 H, J = 10.0, 2.7, 1.3) ; ^{13}C NMR (75 MHz, $CDCl_3$)δ: 25.3, 36.6, 38.9, 65.1, 130.2, 151.5, 199.9 ; mass spectrum (EI) 126 ($C_7H_{10}O_2$); 96 (base).

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

Aminosiloxy dienes have been found to exhibit unusually high reactivity in Diels-Alder reactions with a wide range of electron-deficient dienophiles.[2,3] [4] [5] Determination of the second order rate constants with methacrolein showed the parent aminosiloxy diene to be about 10^3 more reactive than the analogous 1-alkoxy-3-siloxy diene.[4] The reactions of aminosiloxy dienes with various dienophiles occur under mild conditions and afford the corresponding cycloadducts in high yields and with complete regioselectivity. An extensive study on the preparation and cycloadditions of amino siloxy dienes has been carried out.[3]

The three-step procedure above illustrates the usefulness of a 1-amino-3-siloxy diene for the synthesis of functionalized cyclohexenones and is representative of the general usefulness of the dienes. The first step in the sequence, the Diels-Alder reaction between the parent aminosiloxy diene and methyl acrylate , cleanly produces the cycloadduct, as a mixture of endo and exo diastereomers. This diene also reacts with many other dienophiles and the results are summarized in Table I.[3] The cycloadducts are generally obtained as mixtures of endo-exo diastereomers, except for the reactions with N-phenylmaleimide and methacrolein , which proceed with high endo selectivity, and with dimethyl maleate , which gives predominantly the exo adduct.

The products of the Diels-Alder reactions of aminosiloxy dienes are versatile synthetic intermediates, as they can be subjected to reduction, Wittig olefination, or deprotonation without any hydrolysis or elimination.[2,3] On the other hand, it is possible under acidic conditions both to hydrolyze the silyl enol ether and β-eliminate the amino group to afford the corresponding enones.

The usefulness of aminosiloxy diene Diels-Alder chemistry to the preparation of different substituted cyclohexenones is demonstrated in Table II.[3] The functionality at the 4 and 5-positions of the cyclohexenones can be easily controlled by the substitution pattern in the dienophile. The differing endo-exo selectivity found in the initial cycloadducts does not impact the usefulness of this route to cyclohexenones, since the amino group is eliminated in the last step. Chiral versions of aminosiloxy dienes provide the opportunity for asymmetric synthesis. Indeed, the diphenylpyrrolidine-substituted diene allows the synthesis of a variety of cyclohexenones, with good to excellent ee's.[2b] The usefulness of aminosiloxy diene Diels-Alder reactions to natural product synthesis is exemplified through the stereocontrolled synthesis of the pentacyclic indole alkaloid tabersonine.[2c]

Table I

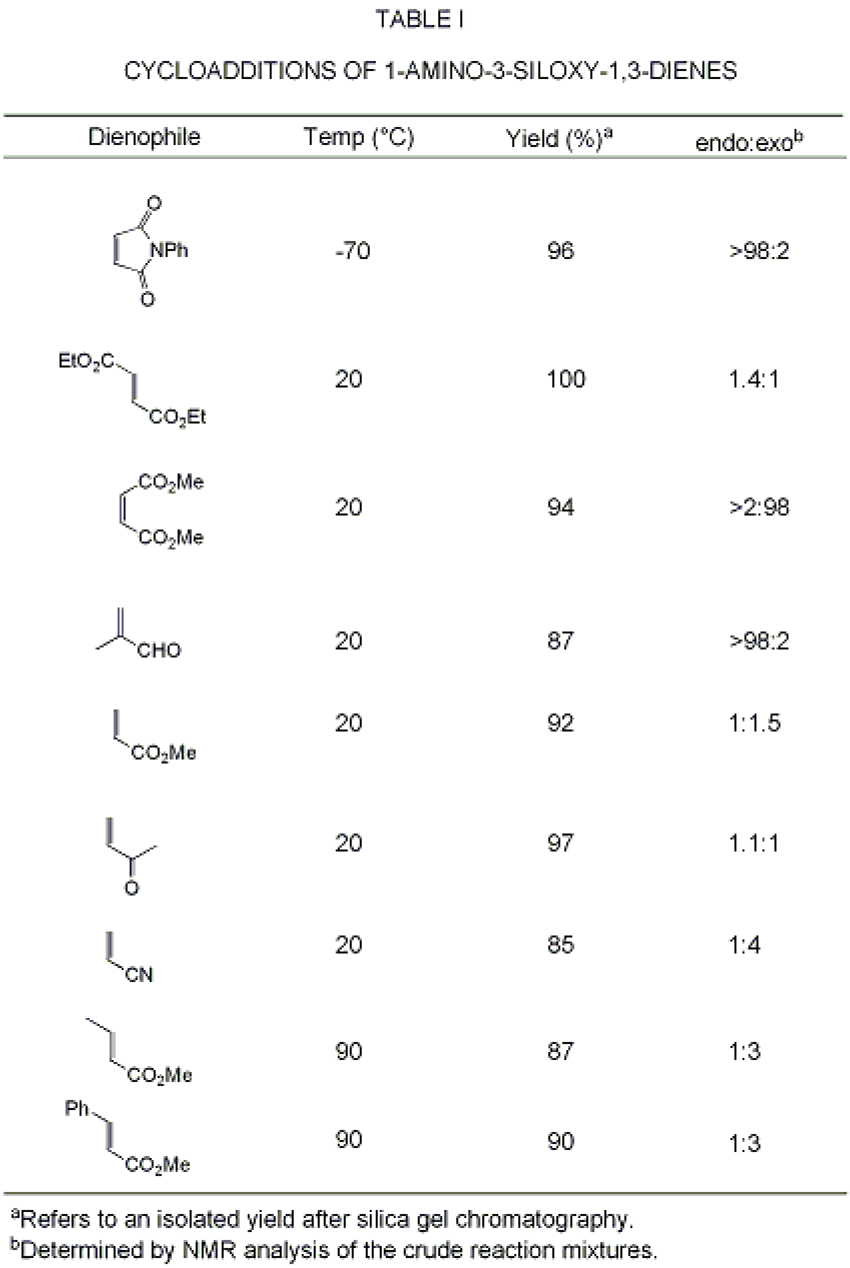


TABLE I

CYCLOADDITIONS OF 1-AMINO-3-SILOXY-1,3-DIENES

Dienophile	Temp (°C)	Yield (%)[a]	endo:exo[b]
O NPh O	-70	96	>98:2
EtO_2C CO_2Et	20	100	1.4:1
CO_2Me CO_2Me	20	94	>2:98
CHO	20	87	>98:2
CO_2Me	20	92	1:1.5
O	20	97	1.1:1
CN	20	85	1:4
CO_2Me	90	87	1:3
Ph CO_2Me	90	90	1:3

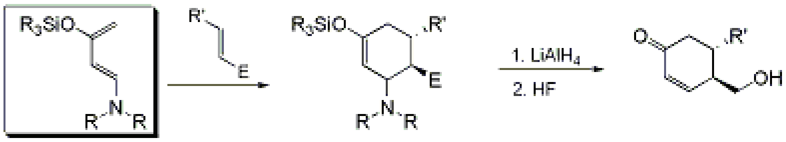
[a] Refers to an isolated yield after silica gel chromatography.

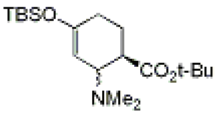
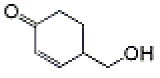
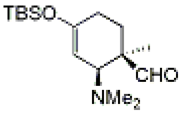
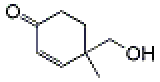
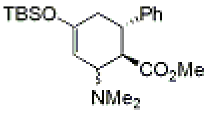
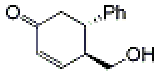
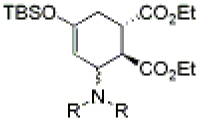
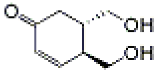
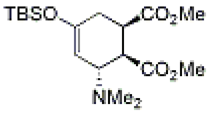
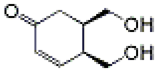
[b] Determined by NMR analysis of the crude reaction mixtures.

Table II

TABLE II

PREPARATION OF SUBSTITUTED CYCLOHEXENONES



Entry	Cycloadduct	Product	Overall Yield (%)
1			90
2			85
3			86
4			82
5			85

References and Notes

1. Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, IL 60637.
2. (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252; (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165; (c) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

(E)-1-Dimethylamino-3-tert-butyldimethylsiloxy-1,3-butadiene:
1,3-Butadien-1-amine, 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-N,N-dimethyl-, (E)- (14); (194233-66-4)

Methyl acrylate:
Acrylic acid, methyl ester (8);
2-Propenoic acid, methyl ester (9); (96-33-3)

4-Hydroxymethyl-2-cyclohexen-1-one:
2-Cyclohexen-1-one, 4-(hydroxymethyl)-, (14); (224578-91-0)

4-Carbomethoxy-3-dimethylamino-1-tert-butyldimethylsiloxy-1-cyclohexene:
3-Cyclohexene-1-carboxylic acid, 2-(dimethylamino)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, methyl ester, (14); cis- (194233-86-8); trans- (194233-84-6)

Lithium aluminum hydride:
Aluminate(1-), tetrahydro-, lithium (8);
Aluminate(1-), tetrahydro-, lithium (T-4)- (9); (16853-85-3)

Hydrofluoric acid: CORROSIVE: (8,9); (7664-39-3)