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.

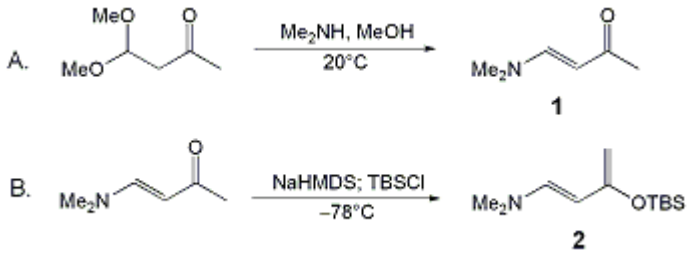
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.078.0152

Organic Syntheses, Coll. Vol. 10, p.301 (2004); Vol. 78, p.152 (2002).

PREPARATION OF (E)-1-DIMETHYLAMINO-3-tert-BUTYLDIMETHYLSILOXY-1,3-BUTADIENE

[1,3-Butadien-1-amine, 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-N,N-dimethyl-]



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

1. Procedure

A. (E)-4-Dimethylamino-3-buten-2-one , **1**.[2] A 250-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with acetylacetaldehyde dimethyl acetal (Note 1) (19.8 g, 0.15 mol), freshly distilled prior to use (67°C, 12 mm). A 2.0 M solution of dimethylamine in methanol (Note 1) (85 mL, 0.17 mol) is then added in one portion. The resulting yellow solution is stirred at room temperature for 4 hr, and concentrated on a rotary evaporator. The resulting oil is purified by bulb-to-bulb distillation (0.25 mm, oven temp 100-120°C) (Note 2) to afford 15.3 g (90%) of the desired vinylogous amide as a pale-orange oil (Note 3).

B. (E)-1-Dimethylamino-3-tert-butyldimethylsiloxy-1,3-butadiene , **2**. A dry, 500-mL, three-necked, round-bottomed flask is equipped with a pressure equalizing addition funnel, a large egg-shaped magnetic stirring bar, and a nitrogen/vacuum adapter. The apparatus is evacuated and flushed with nitrogen. The flask is charged with a 1.0 M solution of sodium bis(trimethylsilyl)amide (NaHMDS) in tetrahydrofuran (THF) (Note 1) (100 mL, 0.100 mol) and the flask is cooled in a dry ice-acetone bath (−70°C bath temp), causing a viscous, yellowish-white suspension to form. To this suspension is added, over a period of 30 min via an addition funnel, a solution of (E)-4-dimethylamino-3-buten-2-one (11.3 g, 0.100 mol) in THF (50 mL). The funnel is rinsed with a small amount of THF, and the resulting clear-yellow solution is stirred for 1.0 hr at −78°C. A solution of tert-butylchlorodimethylsilane (Note 4) (15.8 g, 0.105 mol) in THF (50 mL) is added over a 5-min period, via an addition funnel. The funnel is again rinsed with a small amount of THF. The cooling bath is removed and the reaction mixture is allowed to reach room temperature, which requires about 1.5 hr. The reaction mixture is poured into a 1-L Erlenmeyer flask containing 600 mL of anhydrous ether (Note 5). The resulting suspension is allowed to stand for 30 min and then suction filtered through a pad of dry Celite (60 g) (Note 6) packed in a 600-mL sintered glass filter funnel (Note 7). The filter cake is washed with three 50-mL portions of ether (Note 8), and the filtrate is concentrated on a rotary evaporator (heating bath temp <45°C). The resulting dark orange oil, containing the diene and hexamethyldisilazane, is subjected to bulb-to-bulb distillation (110-120°C, 0.3 mm) (Note 9) to yield 20.4 g (90%) of the desired 1-amino-3-siloxy-1,3-butadiene (Note 10) as a light-yellow oil (Note 10).

2. Notes

1. This reagent was purchased from the Aldrich Chemical Company, Inc.
2. The receiver bulb was cooled with ice as soon as the product started to distill.
3. On occasion the vinylogous amide was obtained as a dark oil, but exhibited good spectroscopic properties. A cleaner-looking sample of the product was obtained by resubjecting the dark oil to bulb-to-bulb distillation. The checkers used a coffee-maker bulb-to-bulb distillation apparatus and recorded a bp of 60-80°C at 0.1 mm. Characterization data follow: IR (neat) cm^{-1}: 1660, 1575, 1436, 1356, 1258,

1112, 962 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.10 (s, 3 H), 2.88 (br s, 3 H), 2.99 (br s, 3 H), 5.05 (d, 1 H, J = 12.8), 7.47 (d, 1 H, J = 12.8) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.0, 36.9, 44.5, 96.6, 152.6, 195.2 ; mass spectrum (EI) 113 ($C_6H_{11}NO$), 98 (base) .
4. This reagent was purchased from Lithco, a division of the FMC Corporation.
5. Anhydrous ether was purchased from Fisher Scientific Company and used without further purification.
6. Celite 545 was purchased from Fisher Scientific Company and was flame-dried under vacuum just prior to filtration. The Celite was packed tightly into the funnel using the bottom of a beaker.
7. A sintered-glass Büchner funnel having a C-porous frit was employed.
8. When the filtration became very slow, the filter cake was stirred with a spatula to break up the pasty layer on top. The filtration must be done carefully to minimize transfer of sodium chloride (NaCl) to the filtrate. Lower yields of less pure product are obtained if considerable amounts of NaCl are present during the subsequent distillation. If a gel is obtained after removal of solvent on the rotary evaporator, too much NaCl is present.
9. A 250-mL flask is used as the pot, connected to a 100-mL collection bulb, connected to a cold trap (dry ice-acetone) to protect the vacuum pump. Hexamethyldisilazane is collected first in the cold finger (−78°C). Then, as soon as the diene starts to distill, the collection bulb is cooled with ice. The checkers recorded a bp of 60-80°C at 0.07 mm.
10. The diene displays the following spectral data: IR (neat) cm^{-1}: 1648 ; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.19 (s, 6 H), 0.98 (s, 9 H), 2.70 (s, 6 H), 3.84 (s, 1 H), 3.92 (s, 1 H), 4.78 (d, 1 H, J = 13.2), 6.57 (d, 1 H, J = 13.2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.6, 18.3, 25.9, 40.5, 85.8, 95.9, 140.9, 156.4 ; mass spectrum (EI) 227 ($C_{12}H_{25}NOSi$), 156 (base) . This material contains trace impurities by ^{1}H and ^{13}C NMR.
11. The submitters report that an alternate purification method involves distillation through a micro short-path distillation apparatus fittted with a Vigreux column (10 cm). Under this protocol, diene **2** (bp 60°C at 0.5 mm) is obtained as a clear, colorless liquid in 82% yield. (This modification was not checked).

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

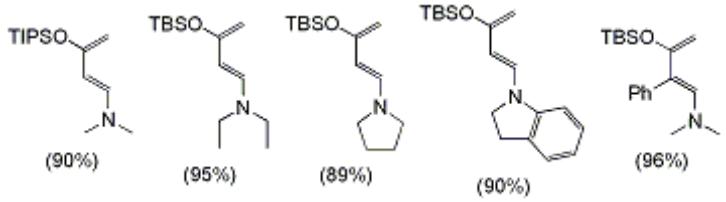
The usefulness of the Diels-Alder reaction continues to grow as new dienes and dienophiles are developed.[3] For the normal demand Diels-Alder reaction, it is well recognized that electron-donating groups render a diene more reactive toward electron-poor dienophiles. Moreover, the cycloadditions take place with excellent regioselectivity and give products possessing useful functional groups.[4] The submitters recently reported the development of 1-amino-3-siloxy-1,3-butadienes, a new class of highly-reactive heteroatom-containing dienes.[5] Clearly related to dialkoxybutadienes such as the widely used 1-methoxy-3-trimethylsiloxy-1,3-butadiene, known also as Danishefsky's diene,[6] the 1-amino-3-siloxy-1,3-butadienes possess several properties that make them synthetically attractive. They are conveniently prepared, as illustrated above, by deprotonation of readily available vinylogous amides with potassium bis(trimethylsilyl)amide (KHMDS) or NaHMDS, followed by silylation of the corresponding enolates. The dienes also exhibit very high reactivity toward a wide range of dienophiles.[5,7]

The submitters have investigated several procedures for the preparation of vinylogous amide **1**, the precursor to the aminosiloxydiene. They first prepared this compound by an Eschenmoser sulfide contraction between dimethylthioformamide and bromoacetone.[5a] While effective, the procedure was not convenient for the preparation of multigram quantities of the vinylogous amide, because of the difficulty associated with removal of the triphenylphosphine sulfide by-product. A better alternative is to react a secondary amine with 4-methoxy-2-butenone.[7] This addition-elimination proceeds well with a wide range of secondary amines. The cost associated with 4-methoxy-2-butenone prompted the investigation of acetylacetaldehyde dimethyl acetal as a starting material. Not only can this compound be converted to 4-methoxy-2-butenone, but it can also be treated directly with secondary amines to yield the desired vinylogous amide. Clean 4-methoxy-2-butenone can be distilled in 89% yield by heating

acetylacetaldehyde dimethyl acetal containing a catalytic amount of NaOAc to 160-170°C. The procedure described above was adapted from that reported by Maggiulli and Tang.[2]

The second step in the above sequence, deprotonation followed by silylation of the resulting enolate, was not successful under standard lithium diisopropylamide (LDA) conditions, presumably because silylation of the lithium enolate was slow. The deprotonation/silylation can be carried out effectively using KHMDS, which is available from Aldrich Chemical Company, Inc., as a 0.5 M solution in toluene. This protocol is quite general for the preparation of various dienes containing different silyl and amino groups as illustrated in Table I.[5,7] For preparative scale reactions, such as that described above, the use of NaHMDS was preferred as it is available from Aldrich Chemical Company, Inc., as 1.0 M solution in THF. The procedure described here also provides a convenient and high-yielding preparation of Danishefsky's diene (1-methoxy-3-trimethylsiloxy-1,3-butadiene).[8]

TABLE I
PREPARATION OF VARIOUS 1-AMINO-3-SILOXY-1,3-DIENES



Aminosiloxy dienes are highly reactive in Diels-Alder reactions, considerably more so than the analogous dialkoxy dienes.[5a, 9] They undergo [4+2] cycloadditions with a broad range of electron-deficient dienophiles.[5,7] The reactions generally occur under very mild conditions and afford the corresponding cycloadducts in good yields and with complete regioselectivity. A full study on the preparation and cycloadditions of amino siloxy dienes has been carried out.[7] In the procedure that follows, a preparative scale procedure is described for the Diels-Alder reaction of an aminosiloxy diene, reduction of the electron-withdrawing group in the adduct, and hydrolysis of the β-aminoenolsilyl ether moiety to the 4-substituted cyclohexenone.

References and Notes

1. Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, IL 60637.
2. Maggiulli, C. A.; Tang, P.-W. *Org. Prep. Proc. Int.* **1984**, *16*, 31.
3. Oppolzer, W. In "Comprehensive Organic Synthesis"; Pergamon Press: New York, 1991; Vol. 5, pp. 315-400.
4. (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753; (b) Fringuelli, F.; Taticchi, A. "Dienes in the Diels-Alder Reaction"; Wiley: New York, 1990.
5. (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; (d) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562.
6. Reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400; (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15; (c) Danishefsky, S. *Chemtracs: Org. Chem.* **1989**, *2*, 273.
7. Kozmin, S. A.; Janey, J. M.; Rawal, V. H., *J. Org. Chem.* **1999**, *64*, 3039.
8. Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth., Coll. Vol. VII* **1990**, 312.
9. Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045.

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)

(E)-4-Dimethylamino-3-buten-2-one:
3-Buten-2-one, 4-(dimethylamino)- (E)-; (2802-08-6)

Acetylacetaldehyde dimethyl acetal:
2-Butanone, 4,4-dimethoxy- (9); (5436-21-5)

Dimethylamine (8);
Methanamine, N-methyl- (9); (124-40-3)

Sodium bis(trimethylsilyl)amide: NaHMDS:
Disilazane, 1,1,1,3,3,3-hexamethyl-, sodium salt (8);
Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, sodium salt (9); (1070-89-9)

tert-Butyldimethylsilyl chloride: CORROSIVE:
Silane, chloro(1,1-dimethylethyl)dimethyl- (9); (18162-48-6)