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.

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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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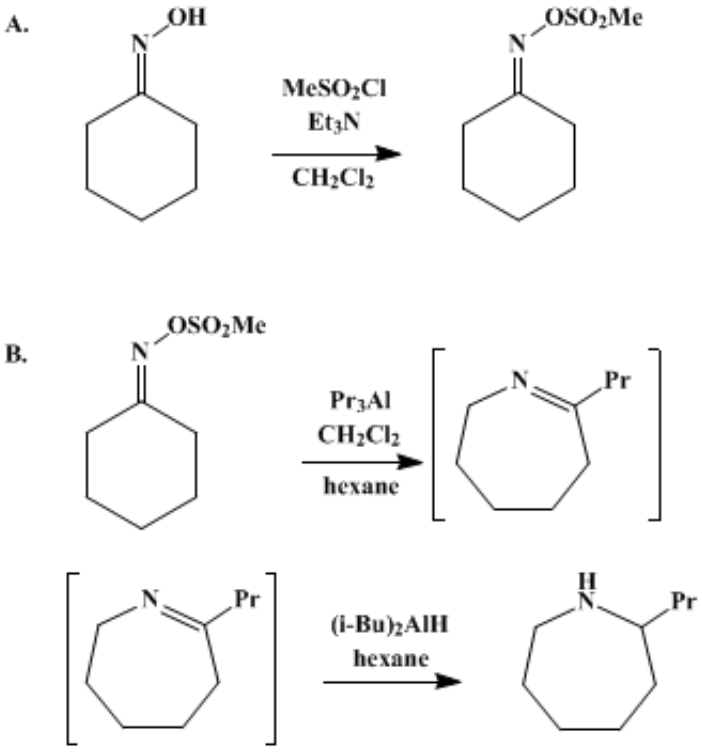
2-PROPYL-1-AZACYCLOHEPTANE FROM CYCLOHEXANONE OXIME

[1*H*-Azepine, hexahydro-2-propyl-, (±)-]



Submitted by Keiji Maruoka, Shuichi Nakai, and Hisashi Yamamoto[1].
Checked by Jeffrey Doney and Clayton H. Heathcock.

1. Procedure

Caution! Dialkylzinc compounds, especially in undiluted form, are pyrophoric and must not be allowed to come into contact with air or moisture. These compounds should only be handled by individuals trained in their proper and safe use. [Note added January 2011]

Caution! Part B of this procedure should be carried out in a well-ventilated hood to prevent exposure to methanethiol, a side product.

A. *Cyclohexanone oxime methanesulfonate.* A dry, 1-L, two-necked, round-bottomed flask is equipped with a gas inlet, a rubber septum, and a magnetic stirring bar. The flask is charged with 17.0 g (0.15 mol) of cyclohexanone oxime (Note 1) and flushed with argon, after which 300 mL of dichloromethane followed by 25 mL (0.18 mol) of triethylamine (Note 2) are injected through the septum into the flask. The solution is stirred and cooled to a temperature of −15 to −20°C in a dry ice–carbon tetrachloride bath, while 12.8 mL (0.165 mol) of methanesulfonyl chloride is added over a 20-min period (Note 3) and (Note 4). The resulting mixture is stirred at this temperature for 15 min, and poured into 300 mL of ice water in a 1-L separatory funnel with the aid of three 30-mL portions of dichloromethane to rinse the flask. The lower organic layer is separated, and the aqueous layer is extracted with a 50-mL portion of dichloromethane. The combined extracts are washed successively with 250 mL of cold aqueous 10% hydrochloric acid, 250 mL of saturated sodium bicarbonate, and 250 mL of brine, and are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator at room temperature to

give 27.2–28.8 g of crude solid cyclohexanone oxime methanesulfonate (Note 5). This material is used in Part B without purification (Note 6).

B. *2-Propyl-1-azacycloheptane*. A dry, 2-L, three-necked, round-bottomed flask is equipped with a variable-speed mechanical stirrer, 300-mL pressure-equalizing dropping funnel bearing a gas inlet at its top, and a rubber septum. The apparatus is flushed with argon, after which 243 mL of hexane (Note 7) and 57 mL (0.3 mol) of tripropylaluminum (Note 8) are injected through the septum into the flask. The solution is stirred and cooled to a temperature of −73 to −78°C in a dry ice–methanol bath. The crude cyclohexanone oxime methanesulfonate prepared in Part A is dissolved in 100 mL of dichloromethane, transferred to the dropping funnel, and added to a 1 *M* solution of tripropylaluminum in hexane over a 30-min period (Note 9). The mixture is allowed to warm to 0°C and stirred for 1 hr, and 225 mL (0.225 mol) of 1 *M* solution of diisobutylaluminum hydride in hexane (Note 10) is added at 0°C and the mixture is further stirred at 0°C for 1 hr (Note 11). After addition of 100 mL of dichloromethane and 88.2 g (2.1 mol) of sodium fluoride, 28.4 mL (1.58 mol) of water is injected dropwise at 0°C (Note 12). Vigorous stirring of the resulting suspension is continued for 30 min at room temperature, and the contents of the flask are filtered with five 30-mL portions of dichloromethane (Note 13). The combined filtrates are evaporated under reduced pressure with a rotary evaporator. Distillation of the residual liquid under reduced pressure affords 11.3–12.2 g (53–58%) of 2-propyl-1-azacycloheptane as a colorless liquid, bp 79–81°C (18 mm) (Note 14) and (Note 15).

2. Notes

1. Reagent-grade cyclohexanone oxime, purchased from Wako Pure Chemical Industries, Ltd. (Japan), was used as received. The checkers used material obtained from the Aldrich Chemical Company, Inc. A suitable material may be prepared according to the procedures in *Organic Syntheses*.[2]
2. Both reagent-grade dichloromethane and triethylamine were dried and stored over Linde 4A molecular sieves.
3. The solution turns to a white suspension after half of the methanesulfonyl chloride is added; methanesulfonyl chloride, available from Tokyo Kasei Kogyo Company, Ltd. (Japan), was used without any purification.
4. The checkers found that an addition time of 40 min is required to maintain the temperature of the reaction mixture below −15°C.
5. If a crude oil was obtained at this stage, it can be solidified by cooling.
6. The reaction in Part A proceeds in almost quantitative yield.[3] Accordingly, the crude cyclohexanone oxime methanesulfonate can be used without any purification. Prolonged standing at room temperature may cause serious decomposition. The crude material may be stored in a freezer, or as a dichloromethane solution in a refrigerator, and can be recrystallized from ether-hexane to give the white solid (mp 43–45°C).[4]
7. Reagent-grade hexane was dried and stored over sodium.
8. Neat tripropylaluminum of 96% purity was supplied in a metal cylinder from Toso-Akzo Chemical Company, Ltd. (Japan). This reagent is contaminated by 1.2% of triethylaluminum, 2.2% of triisobutylaluminum, and other compounds. Neat tripropylaluminum is also available from Aldrich Chemical Company, Inc. Since neat tripropylaluminum is pyrophoric and reacts violently with oxygen and water, the syringe should be washed with hexane immediately after addition.
9. The checkers found that an addition time of 60 min is required to maintain the temperature of the reaction mixer below −73°C.
10. Diisobutylaluminum hydride in hexane was available from Aldrich Chemical Company, Inc. and Kanto Chemical Company, Inc. (Japan).
11. Methanethiol is generated as a side product by the reduction of the methanesulfonate with diisobutylaluminum hydride.
12. To avoid excessive foaming at the beginning of the hydrolysis, water should be added carefully by syringe. The rate of addition may be increased once the initially vigorous foaming subsides.
13. The sodium fluoride–water workup offers an excellent method for large-scale preparations and is generally applicable for product isolation in the reaction of organoaluminum compounds.[5]
14. The elemental analysis and the spectral properties of the product are as follows. Anal. calcd. for $C_9H_{19}N$: C, 76.61; H, 13.47; N, 9.92. Found: C, 76.75; H, 13.74; N, 9.51; IR (liquid film) cm^{-1}: 3320,

2860–2970, 1460, 1165; ^{1}H NMR ($CDCl_3$) δ: 0.87–0.94 (3 H, m, CH_3), 1.23–1.82 (13 H, m), 2.54–2.73 (2 H, m, CH_2N), 2.96–3.03 (1 H, m, CHN). A boiling point of 193–194°C at 750 mm has been reported for 2-propyl-1-azacycloheptane.[6]

15. Gas chromatographic analysis using a 25-m PEG-HT capillary column at 80°C indicated a purity of 97% (retention time: 8.1 min) based on tripropylaluminum of 96% purity (Note 8). The unrearranged product, cyclohexylpropylamine (retention time: 6.9 min), was less than 1%.

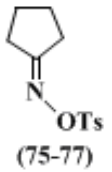
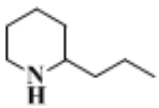
3. Discussion

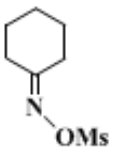
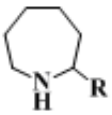
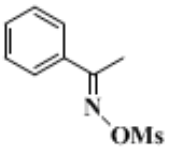
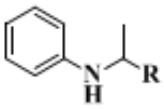
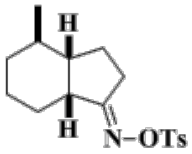
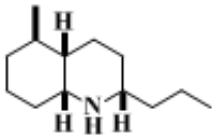
This procedure illustrates a new, general method for the one-nitrogen ring expansion of cyclic ketoximes leading to α-alkylated, cyclic, secondary amines.[4,7] The key step in the sequence is the organoaluminum-promoted Beckmann rearrangement of ketoxime derivatives, in which the organoaluminum compounds are used as amphophilic reagents to induce the Beckmann rearrangement of oxime derivatives as well as to capture the intermediary imino carbocation by the alkyl group that is originally attached to aluminum. The conventional process for accomplishing this transformation consists of the following steps: (a) Beckmann rearrangement of ketoxime or its derivative to lactam; (b) conversion of the lactam to imino ether using trialkyloxonium tetrafluoroborate; (c) alkylation of the imino ether with alkyllithium or Grignard reagent to produce imine, which requires a considerably longer time for execution.[8]

As oxime derivatives, oxime sulfonates can be used preferentially for the following reasons: (a) they are readily available from oximes using *p*-toluenesulfonyl chloride or methanesulfonyl chloride in the presence of base in almost quantitative yield; (b) they are easy to handle because of their fine crystalline properties; and (c) they are sufficiently reactive to initiate the rearrangement by organoaluminum reagents.

As shown in Table I, this reaction sequence has a wide generality and is readily applicable to the straightforward synthesis of various naturally occurring alkaloids such as coniine,[9] pumiliotoxin C,[10] and solenopsin A and B.[11] Oxime sulfonates of either linear or cyclic structures may be used. Obviously, the regioselectivity of the reaction follows the general rule of the Beckmann rearrangement,[12] and preferential migration of the group *anti* to the oxime sulfonate is observed. Diethylaluminum alkynides can be successfully used for the selective introduction of alkynyl groups to a substrate in preference to an ethyl group. Furthermore, the present procedure reduces the intermediate imine directly without isolation by using diisobutylaluminum hydride, thus excluding the troublesome isolation of unstable cyclic imino compound.

TABLE I
PREPARATION OF α-ALKYLATED AMINES FROM OXIME SULFONATES WITH TRIALKYLALUMINUM–DIISOBUTYLALUMINUM HYDRIDE

Oxime Sulfonate (mp, °C)	Trialkylaluminum	Amine	Yield (%)
 (75-77)	Pr_3Al[a]		55-58
	Me_3Al		70 (R = Me)

 (43-45)	$Et_2AlC{\equiv}CBu$		67 (R = C≡CBu)
	Me_3Al		67 (R = Me)
 (64-65)	$Et_2AlC{\equiv}CBu$		83 (R = C≡CBu)
	$Et_2AlC{\equiv}CPh$		67 (R = C≡CPh)
 (67-71)	Pr_3Al[b]		60

[a]Treatment with Pr_3Al at 40–80°C for 15–30 min.

[b]Treatment with Pr_3Al at 25°C for 30 min.

The organoaluminum-promoted Beckmann rearrangement–alkylation sequence represents a modern aspect of the classical Beckmann rearrangement, and has proved effective with other aluminum reagents of type R_2AlX (X = SR, SeR, CN) which would function in a similar way to trialkylaluminum compounds. Thus, a series of imino thioethers, selenoethers, and nitriles can be prepared with rigorous regioselectivity by using organoaluminum thiolates, selenolates, and cyanide, respectively.[4]

2-Propyl-1-azacycloheptane has been prepared by reduction of 2-aza-1-oxo-3-propylcycloheptane with lithium aluminum hydride,[6] and from azacycloheptane by conversion to its formamidine, alkylation with 1-iodopropane, and subsequent hydrazinolysis.[13]

References and Notes

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

brine

2-aza-1-oxo-3-propylcycloheptane

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

sodium (13966-32-0)

dichloromethane (75-09-2)

Cyclohexanone oxime (100-64-1)

methanethiol (74-93-1)

sodium fluoride (7681-49-4)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

argon (7440-37-1)

triisobutylaluminum (100-99-2)

Methanesulfonyl chloride (124-63-0)

diisobutylaluminum hydride (1191-15-7)

triethylaluminum (97-93-8)

p-Toluenesulfonyl chloride (98-59-9)

methanesulfonate

1-iodopropane (107-08-4)

azacycloheptane (111-49-9)

2-Propyl-1-azacycloheptane,
1H-Azepine, hexahydro-2-propyl-, (±)- (85028-29-1)

Cyclohexanone oxime methanesulfonate (80053-69-6)

tripropylaluminum

cyclohexylpropylamine