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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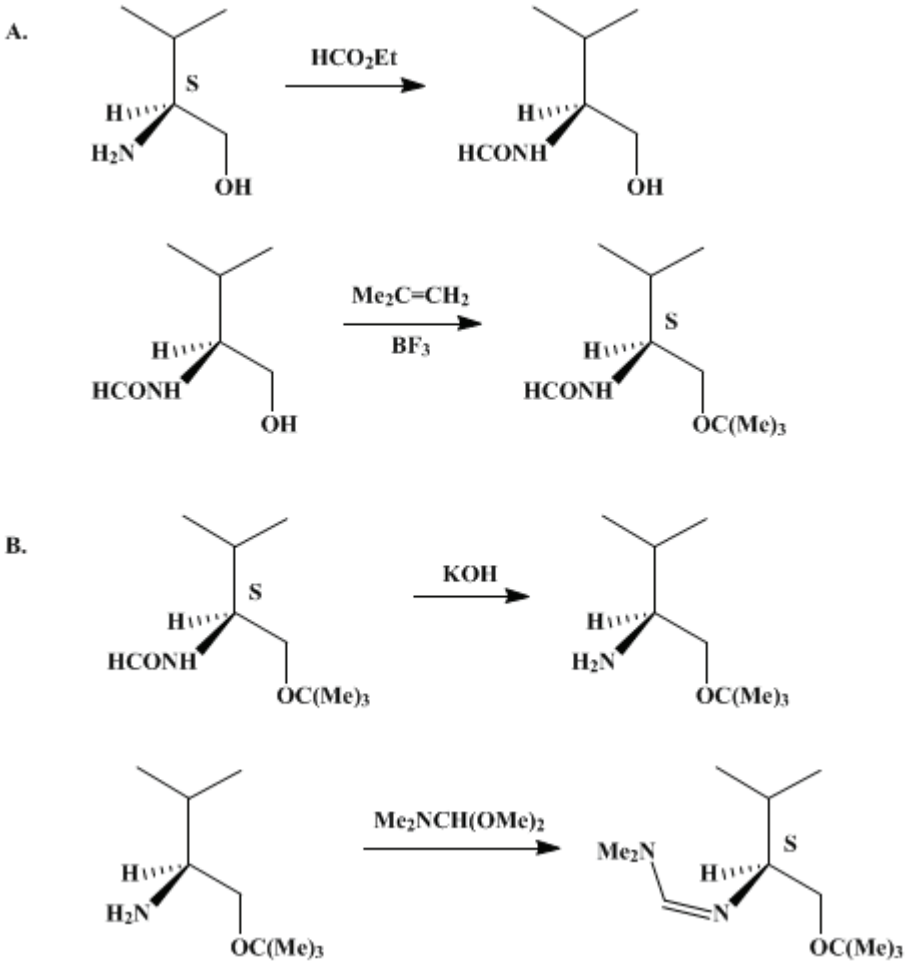
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.067.0052

Organic Syntheses, Coll. Vol. 8, p.204 (1993); Vol. 67, p.52 (1989).

(*S*)-*N*,*N*-DIMETHYL-*N*′-(1-*tert*-BUTOXY-3-METHYL-2-BUTYL) FORMAMIDINE

[Methanimidamide, *N*′-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-*N*,*N*-dimethyl-, (*S*)-]



Submitted by Daniel A. Dickman, Michael Boes, and Albert I. Meyers[1].
Checked by Jeffrey Romine and Leo A. Paquette.

1. Procedure

A. *(S)-N-Formyl-O-tert-butylvalinol (1)*. In a 100-mL, round-bottomed flask, 20.6 g (200 mmol) of (*S*)-valinol (Note 1) and 16 g (216 mmol) of ethyl formate (Note 2) are heated at reflux under a nitrogen atmosphere for 1 hr. Excess ethyl formate is removed under reduced pressure and the oil is triturated with dry ether until a yellow solid appears. This material is dissolved in 260 mL of dry dioxane (Note 3) in a 1000-mL pressure bottle (Note 4) equipped with a magnetic stirring bar and immersed in an ice–water bath. The bottle is immediately charged with ca. 260 mL of liquid isobutene (Note 5) and 75 mL of boron trifluoride etherate is rapidly added. The pressure bottle is sealed with a stopper, removed from the ice bath, and stirred at room temperature for 3 hr (Note 6). In a fume hood, excess isobutene is removed from the resulting clear solution by carefully cracking the seal of the stopper. When the gas ceases to discharge, the stopper is removed and the solution is poured into a 1000-mL separatory funnel containing 250 mL of 2 *N* sodium hydroxide and is extracted twice with 100 mL of dichloromethane. The organic layer is washed with 100 mL of brine and dried over anhydrous magnesium sulfate. The

organic solvent is removed and the residue is distilled (Kugelrohr tube, 0.05 mm, 80–85°C bath temperature) to give 27–36 g (75–95%) of *N*-formyl-*O*-*tert*-butylvalinol **(1)** as a clear oil (Note 7).

B. *(S)-N,N-Dimethyl-N′-(1-tert-butoxy-3-methyl-2-butyl)formamidine* ***(2)***. In a 500-mL, round-bottomed flask 26 g (140 mmol) of the formamide from Part A is dissolved in 100 mL of ethanol and 200 mL of a 50% aqueous potassium hydroxide solution is added. The mixture is heated at reflux overnight; on cooling, the reaction separates into colorless aqueous and organic layers. The two layers are extracted 3 times with 100 mL of ether and the combined organic layers are washed with 100 mL of brine. After the solution is dried over anhydrous potassium carbonate and filtered, the ether and ethanol are carefully removed under aspirator vacuum at ambient temperature. The crude amine is treated with 25 g (210 mmol) of *N,N*-dimethylformamide dimethyl acetal (Note 8) and the reaction mixture is heated under argon at 40°C for 1 hr. The solution is concentrated under reduced pressure and the crude product is distilled bulb-to-bulb (0.05 mm, 55–65°C) to give 25.7–27 g (86–91.5%) of (*S*)-*N,N*-dimethyl-*N′*-(1-*tert*-butoxy-3-methyl-2-butyl)formamidine **(2)** as a colorless liquid (Note 9).

2. Notes

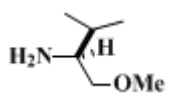
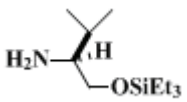
1. (L)- or (*S*)-Valinol was purchased from Aldrich Chemical Company, Inc. and used without further purification. The preparation of (L)-valinol has been described: Smith, G. A.; Gawley, R. E. *Org. Synth., Coll. Vol. VII* **1990**, 530.
2. Ethyl formate was purchased from J. T. Baker Chemical Company.
3. Dioxane was distilled from lithium aluminum hydride.
4. A Kimble bottle (#15096) purchased from VWR Scientific (Cat. No. 16267-101) was employed.
5. Isobutene was purchased from Matheson Gas Products.
6. The two-layer system became a clear solution within 15 min.
7. The physical properties are as follows: IR (neat) cm^{-1}: 3300, 1660; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.79–0.88 (m, 6 H), 1.07 (s, 9 H), 1.82 (m, 1 H), 3.3 (m, 2 H), 3.75 (m, 1 H), 7.94 (d, 1 H, $J = 12$), 8.13 (d, 1 H, $J = 1$); $[\alpha]_D^{25}$ −59.6° (EtOH, c 3.5).
8. *N,N*-Dimethylformamide dimethyl acetal was purchased from Aldrich Chemical Company, Inc.
9. The physical properties are as follows: IR (neat) cm^{-1}: 1660; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.77 (d, 3 H, $J = 6.5$), 0.79 (d, 3 H, $J = 6.5$), 1.07 (s, 9 H), 1.72 (m, 1 H), 2.6–3.5 (m, 3 H), 2.73 (s, 6 H), 7.14 (s, 1 H); $[\alpha]_D^{25}$ −15.9° (THF, c 0.98).

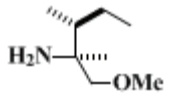
3. Discussion

This procedure for the synthesis of *N,N*-dimethyl-*N′*-alkylformamidines is representative for both chiral and achiral alkyl groups. These compounds are used to activate a wide range of secondary amines toward metalation and alkylation and may be removed to furnish the α-alkylated amines.[2,3]

N,N-Dimethyl-*N′*-alkylformamidines may be prepared from dimethylformamide dimethyl acetal and a primary amine by heating for 1–5 hr[4] (Eq. 1, Table 1).

TABLE I
PREPARATION OF *N,N*-DIMETHYL-*N′*-ALKYLFORMAMIDINES

RNH_2	% yield
	95
	98



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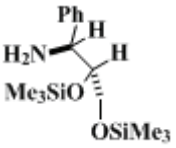
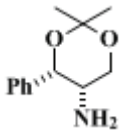


96



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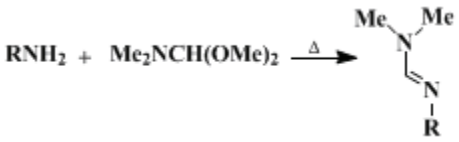
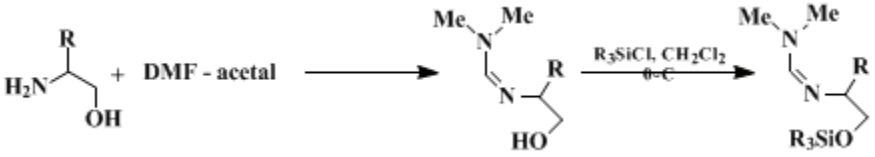


It is also possible to simply heat "DMF-acetal" with an amino alcohol (e.g., valinol, leucinol) and obtain the hydroxy formamidine, which can be directly silylated with Et_3SiCl, Me_3SiCl, or *tert*-$BuMe_2SiCl$ at 0°C in dichloromethane (Eq. 2).[2] If these *N,N*-dimethylformamidines are required, this procedure has the advantage of eliminating the sometimes troublesome cleavage of a silyl ether during reaction with CMF–acetal.



In addition to the exchange reaction[5] described previously,[6] formamidines derived from secondary amines can be prepared by forming the *N*-formyl derivative, which is treated successively with boron trifluoride etherate and the appropriate primary amine[2] (Eq. 3, Table II). However, this method is not satisfactory if sensitive groups (e.g., Me_3Si) are present on the amine since they are cleaved by the Meerwein reagent.

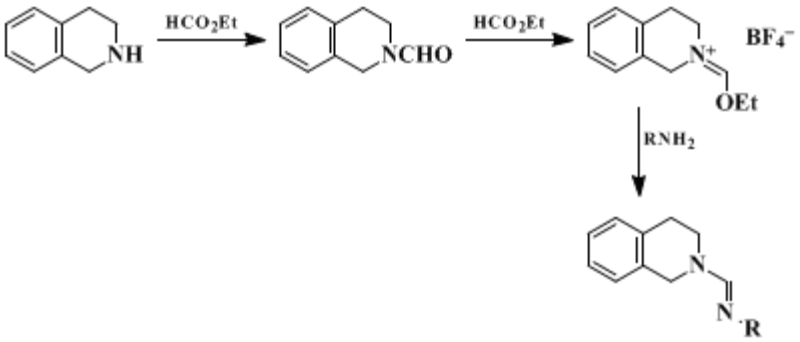
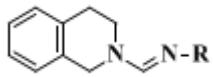
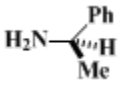
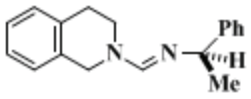


TABLE II
PREPARATION OF FORMAMIDINES
VIA *N*-FORMYL DERIVATIVES

(%)

RNH_2	
	
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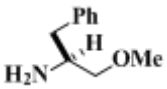
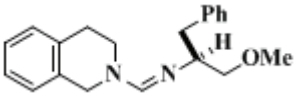
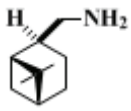
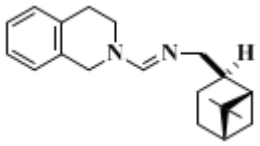
	
94	
	
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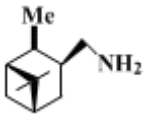	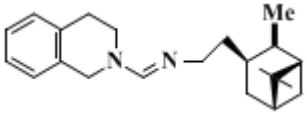
97	

The main advantages of using the *tert*-butyl ether of the valinol formamidine are its stability to reaction conditions used in the asymmetric alkylation of amines and its ready recovery from these reactions for further use.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 573

References and Notes

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2. Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361;
3. Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458.
4. Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.
5. Bredereck, H.; Effenberger, F.; Hofmann, A. *Chem. Ber.* **1964**, *97*, 61.
6. Meyers, A. I.; Boes, M., Dickman, D. A. *Org. Synth., Coll. Vol. VIII* **1993**, 573.

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

brine

(S)-N-Formyl-O-tert-butylvalinol (1)

(S)-N,N-Dimethyl-N'-(1-tert-butoxy-3-methyl-2-butyl)formamidine (2)

(L)- or (S)-Valinol

Et_3SiCl

Me_3SiCl

tert-$BuMe_2SiCl$

N,N-dimethylformamidines

ethanol (64-17-5)

potassium carbonate (584-08-7)

ether (60-29-7)

formamide (75-12-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

ethyl formate (109-94-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

isobutene (9003-27-4)

lithium aluminum hydride (16853-85-3)

argon (7440-37-1)

boron trifluoride etherate (109-63-7)

silyl ether (13597-73-4)

valinol,
(S)-valinol,
(L)-valinol (2026-48-4)

leucinol

dimethylformamide dimethyl acetal,
N,N-dimethylformamide dimethyl acetal (4637-24-5)

hydroxy formamidine

valinol formamidine

tert-butyl ether (6163-66-2)

N-formyl-O-tert-butylvalinol (90482-04-5)

(S)-N,N-DIMETHYL-N'-(1-tert-BUTOXY-3-METHYL-2-BUTYL)FORMAMIDINE,
Methanimidamide, N'-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-N,N-dimethyl-, (S)- (90482-06-7)