



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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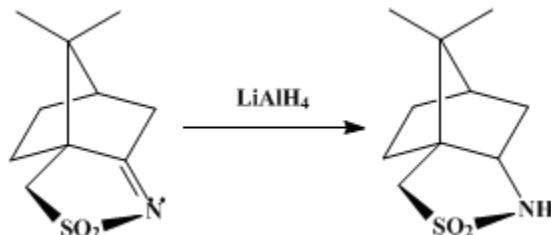
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## (-)-D-2,10-CAMPHORSULTAM

[3*H*-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-2,2-dioxide, (3a*S*)-]



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Checked by David I. Magee and Robert K. Boeckman, Jr..

### 1. Procedure

(-)-2,10-Camphorsultam. A dry, 2-L, three-necked, round-bottomed flask is equipped with a 1.5-in egg-shaped Teflon stirring bar, a 250-mL addition funnel, and a 300-mL Soxhlet extraction apparatus equipped with a mineral oil bubbler connected to an inert-gas source. The flask is charged with 600 mL of dry tetrahydrofuran (THF) (Note 1) and 6.2 g (0.16 mol) of lithium aluminum hydride (Note 2). Into the 50-mL Soxhlet extraction thimble is placed 35.0 g (0.16 mol) of (-)-(camphorsulfonyl)imine (Note 3) and the reaction mixture is stirred and heated at reflux. After all of the (camphorsulfonyl)imine has been siphoned into the reaction flask (3–4 hr), the mixture is allowed to cool to room temperature. The unreacted lithium aluminum hydride is cautiously hydrolyzed by dropwise addition of 200 mL of 1 *N* hydrochloric acid via the addition funnel (Note 4). After the hydrolysis is complete the contents of the flask are transferred to a 1-L separatory funnel, the lower, silver-colored aqueous layer is separated, and the upper layer placed in a 1-L Erlenmeyer flask. The aqueous phase is returned to the separatory funnel and washed with methylene chloride (3 × 100 mL). After the reaction flask is rinsed with methylene chloride (50 mL), the organic washings are combined with the THF phase and dried over anhydrous magnesium sulfate for 10–15 min. Filtration through a 300-mL sintered-glass funnel of coarse porosity into a 1-L round-bottomed flask followed by removal of the solvent on a rotary evaporator gives 33.5 g (95%) of the crude (-)-2,10-camphorsultam. The crude sultam is placed in a 250-mL Erlenmeyer flask and crystallized from approximately 60 mL of absolute ethanol. The product is collected on a 150-mL sintered-glass funnel of coarse porosity and dried in a vacuum desiccator to give 31.1 g (88%) of the pure sultam. A second crop of crystals can be gained by evaporating approximately half the filtrate; the residue is crystallized as above to give 1.4 g (4%). The combined yield of white crystalline solid, mp 183–184°C,  $[\alpha]_D$  −30.7° (CHCl<sub>3</sub>, *c* 2.3) is 92% (Note 5) and (Note 6).

### 2. Notes

1. Tetrahydrofuran (Aldrich Chemical Company, Inc.) was distilled from sodium benzophenone.
2. Lithium aluminum hydride was purchased from Aldrich Chemical Company, Inc.
3. (-)-(Camphorsulfonyl)imine, [(7*S*)-(-)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0<sup>3,7</sup>]dec-3-ene 5,5-dioxide] was prepared by the procedure of Towson, Weismiller, Lal, Sheppard, and Davis, *Org. Synth., Coll. Vol. VIII, 1993, 104*.
4. The addition must be very slow at first (1 drop/5 sec) until the vigorous reaction has subsided.
5. The NMR spectrum of (-)-2,10-camphorsultam is as follows: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 0.94 (s, 3 H, CH<sub>3</sub>), 1.14 (s, 3 H, CH<sub>3</sub>), 1.33 (m, 1 H), 1.47 (m, 1 H), 1.80–2.05 (5 H), 3.09 (d, 1 H, *J* = 14), 3.14 (d, 1 H, *J* = 14), 3.43 (m, 1 H), 4.05 (br s, 1 H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 20.17 (q, CH<sub>3</sub>), 26.51 (t), 31.55 (t), 35.72 (t), 44.44 (d), 47.15 (s), 50.08 (t), 54.46 (s), 62.48 (d).
6. Checkers obtained material having the same mp (183–184°C) and  $[\alpha]_D$  −31.8° (CHCl<sub>3</sub>, *c* 2.3).

### 3. Discussion

(*–*)-2,10-Camphorsultam was first prepared by the catalytic hydrogenation of (*–*)-(camphorsulfonyl) imine over **Raney nickel**.<sup>2</sup> **Lithium aluminum hydride** reduction was used by Oppolzer and co-workers in their synthesis of the sultam.<sup>3,4</sup> However, because of the low solubility of the sultam in **tetrahydrofuran**, a large amount of solvent was required.<sup>4</sup> In the procedure described here the amount of solvent is significantly reduced by using a Soxhlet extractor to convey the imine slowly into the reducing medium.<sup>5</sup>

Oppolzer's chiral auxiliary,<sup>6</sup> (*–*)-2,10-camphorsultam, is useful in the asymmetric Diels–Alder reaction,<sup>3,4</sup> and for the preparation of enantiomerically pure  $\beta$ -substituted carboxylic acids<sup>7</sup> and diols,<sup>8</sup> in the stereoselective synthesis of  $\Delta^2$ -isoxazolines,<sup>9</sup> and in the preparation of *N*-fluoro-(*–*)-2,10-camphorsultam, an enantioselective fluorinating reagent.<sup>10</sup>

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### References and Notes

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

sodium benzophenone

(*–*)-(Camphorsulfonyl)imine

(camphorsulfonyl)imine

(*–*)-2,10-camphorsultam

(*–*)-D-2,10-CAMPHORSULTAM

3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-2,2-dioxide, (3aS)-

*N*-fluoro-(*–*)-2,10-camphorsultam

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Raney nickel (7440-02-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran,  
THF (109-99-9)

lithium aluminum hydride (16853-85-3)

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