



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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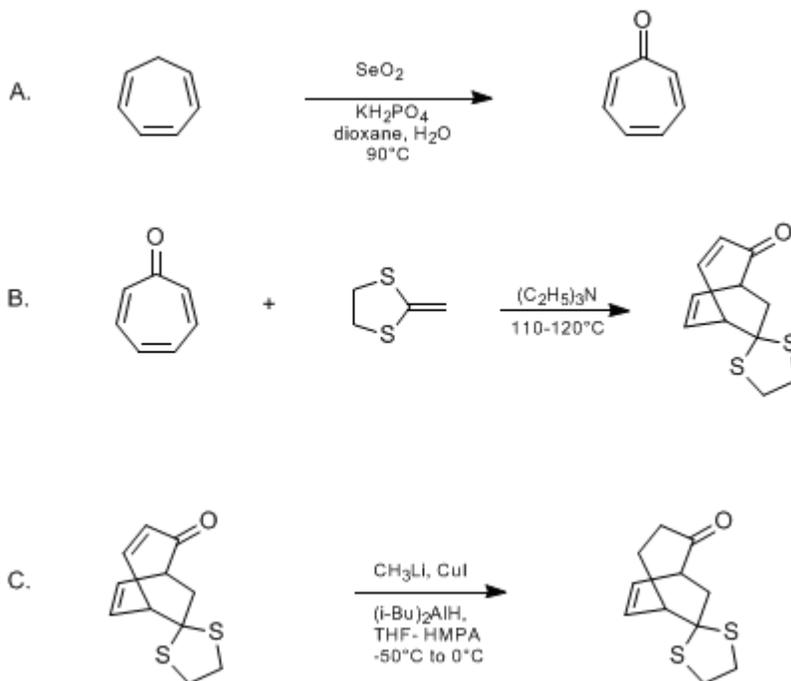
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

Organic Syntheses, Coll. Vol. 9, p.396 (1998); Vol. 71, p.181 (1993).

**INVERSE ELECTRON-DEMAND DIELS-ALDER
CYCLOADDITION OF A KETENE DITHIOACETAL. COPPER
HYDRIDE-PROMOTED REDUCTION OF A CONJUGATED
ENONE. 9-DITHIOLANOBICYCLO[3.2.2]NON-6-EN-2-ONE FROM
TROPONE**



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Checked by Antonino Focella, Mittira Amornmarn, and David L. Coffen.

1. Procedure

A. *Tropone*. A 5-L, three-necked, Morton flask, equipped with a reflux condenser, thermometer, nitrogen inlet, and mechanical stirrer is charged with 81 g (0.59 mol) of potassium dihydrogen phosphate, 200 mL of water, and 2 L of *p*-dioxane. With vigorous mechanical stirring, 258 g (2.80 mol) of cycloheptatriene (Note 1) is added, followed by 318 g (2.87 mol) of selenium dioxide (Note 2). The mixture is heated to 90°C and maintained with vigorous stirring for 20 hr. After the black suspension is cooled to room temperature, 1 L of water is added and the mixture is filtered over Celite (Note 3). The solution is divided into two halves and each is extracted with dichloromethane (2 × 1.5 L). Each organic extract is washed with saturated sodium bicarbonate solution (500 mL) and the solvent is removed under reduced pressure. The combined, crude, black oil is subjected to bulb-to-bulb distillation (20–110°C at 0.05 mm) with dry ice cooling. The resulting light brown liquid is fractionally redistilled (62–65°C at 0.25 mm) to give 147 g (50%) of tropone as a pale yellow oil (Note 4).

B. *9-Dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one*. A 50-mL, three-necked, round-bottomed flask, equipped with a reflux condenser, nitrogen inlet, and magnetic stirring bar is charged with 8.23 g (77.6 mmol) of tropone, 0.75 mL of triethylamine (Note 5), and 11.0 g (93.1 mmol) of 2-methylene-1,3-dithiolane (Note 6). After the system is flushed with nitrogen, the mixture is heated to 110–120°C for 10 hr. The resulting dark oil is cooled to room temperature and purified by column chromatography on silica gel (Note 7). Elution with petroleum ether (1 L) followed by dichloromethane affords 9-dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one as an orange oil that solidifies (10.3 g, 59%), mp 56–58°C (Note 8).

C. 9-Dithiolanobicyclo[3.2.2]non-6-en-2-one. (*Caution! Hexamethylphosphoric triamide (HMPA) is toxic and must be handled with gloves.*) A 500-mL, three-necked, round-bottomed flask, equipped with an argon inlet, stirring bar, thermometer, and rubber septum is charged with 0.80 g (4.2 mmol) of copper(I) iodide (Note 9) and 150 mL of dry tetrahydrofuran (Note 10). The resulting slurry is cooled to -50°C and treated in turn with 3.2 mL of 1.4 M methyllithium in ether (4.5 mmol), 40 mL of hexamethylphosphoramide (Note 11) and (Note 12), and 50 mL of a 1.0 M solution of diisobutylaluminum hydride in hexanes (Note 13), all via syringe. After 1.5 hr at -50°C , 7.4 g (33 mmol) of 9-dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one (Note 14) in 30 mL of tetrahydrofuran is added over 10 min via syringe. The mixture is allowed to warm gradually to 0°C over a 4-hr period and quenched with 75 mL of 1.6 N hydrochloric acid. The organic layer is separated and the aqueous layer is extracted with ether (3×100 mL). The combined organic layers are washed with 1.6 N hydrochloric acid (75 mL), water (3×150 mL), and brine (150 mL), prior to drying over magnesium sulfate. Evaporation of the solvent under reduced pressure yields an orange oil which solidifies on standing for a short time (Note 15). The solid 9-dithiolanobicyclo[3.2.2]non-6-en-2-one thus obtained is vacuum dried to give 6.9 g (92%) of material, mp $68\text{--}71^{\circ}\text{C}$, as one spot on TLC, with no starting material detectable upon NMR analysis (Note 16).

2. Notes

1. Cycloheptatriene was purchased from the Aldrich Chemical Company, Inc., and was washed with 10% sodium hydroxide solution, dried over magnesium sulfate, and distilled prior to use.
2. Selenium dioxide was obtained from Alfa Products, Morton/Thiokol Inc. and used without purification.
3. The solid material containing selenium waste was placed in a container for heavy metal wastes and disposed of by a commercial service according to approved procedures.
4. Spectral characteristics are as follows: IR (CHCl_3) cm^{-1} : 3000, 1630, 1580, 1515, 1470, 1210; ^1H NMR (300 MHz, CDCl_3) δ : 6.88–7.11 (series of m, 6 H).
5. Triethylamine was distilled from calcium hydride prior to use.
6. 2-Methylene-1,3-dithiolane was prepared by the procedure of Dahnke and Paquette, *Org. Synth., Coll. Vol. IX* **1998**, 585.
7. The R_f for this adduct is 0.6 in CH_2Cl_2 . Its presence is clearly visible when anisaldehyde is employed as the staining agent.
8. The adduct exhibits the following spectral properties: IR (CHCl_3) cm^{-1} : 2930, 1665, 1603, 1380, 1165; ^1H NMR (300 MHz, CDCl_3) δ : 2.72 (d, 1 H, $J = 15.5$), 2.87 (dd, 1 H, $J = 6.8, 15.5$), 3.21–3.45 (m, 5 H), 3.66 (t, 1 H, $J = 7.7$), 5.77 (dd, 1 H, $J = 2.0, 11.1$), 6.13 (t, 1 H, $J = 7.9$), 6.60 (dt, 1 H, $J = 0.8, 7.6$), 6.92 (dd, 1 H, $J = 8.5, 11.1$); ^{13}C NMR (75 MHz, CDCl_3) δ : 40.2, 40.6, 42.9, 51.9, 52.1, 70.8, 126.5, 129.4, 139.4, 150.6, 196.3. A sample recrystallized from hexane afforded off-white crystals with mp $62\text{--}63^{\circ}\text{C}$. As an alternative to chromatography, the Diels-Alder adduct can be purified by pouring the cooled, crude product into 100 mL of ether and rinsing the dark viscous gum with additional ether (2×25 mL). The material obtained from evaporation of the combined ethereal extracts is then subjected to bulb-to-bulb distillation. After removal of the volatile impurities, the product distills during the ramping of the temperature from $110\text{--}165^{\circ}\text{C}$ at 0.5 mm. This modification affords a comparable yield of adduct on a 6-fold scale.
9. Copper iodide was purified prior to use by the method of Kauffman.²
10. Tetrahydrofuran was distilled from sodium-benzophenone ketyl before use.
11. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over molecular sieves before use.
12. Attempts were made to substitute other polar solvents for HMPA in this reduction. Under similar reaction conditions but with substitution of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) no reaction took place, and the starting material was recovered unchanged. The slightly more polar 1,3-dimethyl-2-imidazolidinone (DMI) allowed reduction to take place, but with only 80% conversion to a mixture of 1,2- and 1,4-reduction products after 10 hr. With L-selectride in tetrahydrofuran (THF) at -78°C , 1,4-reduction was achieved in 30–60% yield alongside competitive 1,2-reduction.
13. Diisobutylaluminum hydride was purchased from the Aldrich Chemical Company, Inc. and used as received.
14. Before use, this material should be thoroughly dried by heating to 50°C under high vacuum to

constant weight (1–2 hr).

15. The R_f of this product is 0.6 in CH_2Cl_2 . [Anisaldehyde](#) was employed as the staining agent.

16. Spectral characteristics are as follows: IR (CHCl_3) cm^{-1} : 2930, 2860, 1700, 1425; ^1H NMR (300 MHz, CDCl_3) δ : 1.82–1.94 (m, 1 H), 2.28–2.38 (m, 1 H), 2.52–2.70 (m, 3 H), 2.83–2.94 (m, 2 H), 3.10 (t, 1 H, $J = 7.3$), 3.22–3.48 (m, 4 H), 6.14 (t, 1 H, $J = 7.9$), 6.51 (t, 1 H, $J = 8.2$); ^{13}C NMR (75 MHz, CDCl_3) δ : 27.1, 38.1, 39.4, 39.8, 42.9, 46.8, 49.1, 69.9, 127.3, 137.3, 206.9. An analytical sample recrystallized from ether melts at 74–75°C. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{OS}_2$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.32, H, 6.22; S, 28.63.

Waste Disposal Information

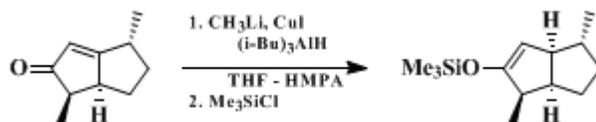
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Although examples of inverse electron-demand Diels-Alder reactions involving ketene thioacetals and α,β -unsaturated aldehydes, ketones, and esters abound,³ the formation of six-membered carbocyclic products is rarely encountered. Isoquinolinium salts and 4a-azoniaanthracenes are recognized as good 2π acceptors,⁴ but the use of positively charged reaction partners is not necessary as the condensation with [tropone](#) illustrates. An important advantage of such cycloadditions is their ability to distinguish two carbonyl groups from the outset. Furthermore, the example provided illustrates the regioselectivity with which carbon-carbon bond formation occurs.

The methodology employed for the oxidation of [cycloheptatriene](#) is based on an original report by Radlick⁵ as subsequently improved by Rigby and Wilson.⁶

The second stage of the procedure describes a method for the fully regiocontrolled saturation of conjugated double bonds in the presence of isolated pi bonds. The agent perhaps responsible for this discrimination is a coordinated form of [copper hydride](#). Although "CuH" has been generated in several different ways, the diisobutylaluminum hydride-methyl copper-HMPA complex developed by Tsuda and Saegusa⁷ is especially attractive because of its quantitative capacity for 1,4-reduction and its ease of generation.⁸ This chemistry results in regioselective enolate anion formation and permits ready trapping of these intermediates as illustrated below:⁹



Consequently, this mild, conjugate reduction may become a powerful tool in synthetic organic chemistry.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 585](#)

References and Notes

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

petroleum ether

brine

9-Dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one

9-Dithiolanobicyclo[3.2.2]non-6-en-2-one

sodium-benzophenone ketyl

diisobutylaluminum hydride-methyl copper-HMPA

[hydrochloric acid \(7647-01-0\)](#)

[ether \(60-29-7\)](#)

[sodium hydroxide \(1310-73-2\)](#)

[sodium bicarbonate \(144-55-8\)](#)

[nitrogen \(7727-37-9\)](#)

[selenium dioxide \(7446-08-4\)](#)

[dichloromethane \(75-09-2\)](#)

[copper\(I\) iodide \(7681-65-4\)](#)

[magnesium sulfate \(7487-88-9\)](#)

[potassium dihydrogen phosphate \(7778-77-0\)](#)

[selenium](#)

[Tetrahydrofuran \(109-99-9\)](#)

[copper iodide \(7681-65-4\)](#)

hexane (110-54-3)

Methylithium (917-54-4)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

cycloheptatriene (544-25-2)

hexamethylphosphoric triamide,
hexamethylphosphoramide (680-31-9)

p-dioxane (123-91-1)

anisaldehyde (123-11-5)

Tropone (492-37-5)

1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7226-23-5)

KETENE DITHIOACETAL

2-Methylene-1,3-dithiolane (26728-22-3)

1,3-dimethyl-2-imidazolidinone (80-73-9)

copper hydride