



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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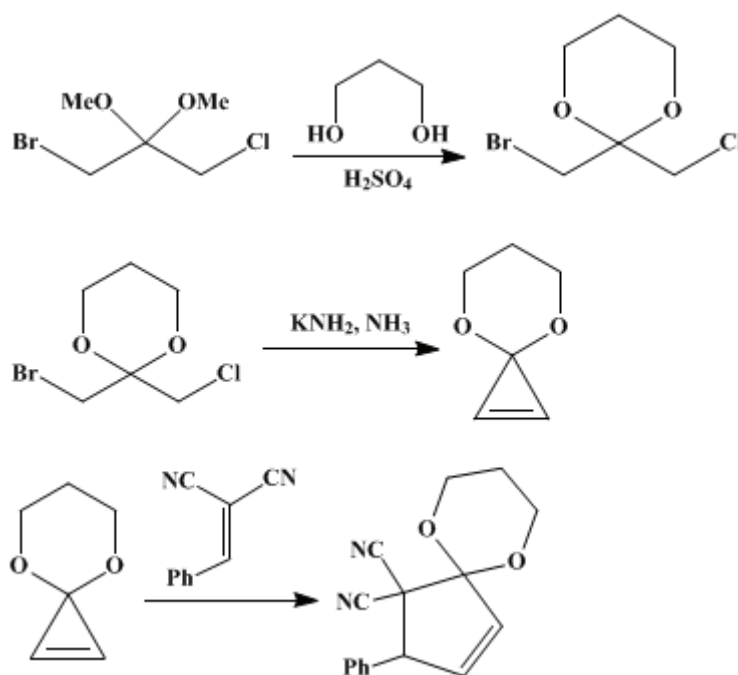
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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**PREPARATION AND THREE-CARBON + TWO-CARBON  
CYCLOADDITION OF CYCLOPROPENONE 1,3-PROPANEDIOL  
KETAL: 5,5-DICYANO-4-PHENYL-2-CYCLOPENTEN-1-ONE 1,3-  
PROPANEDIOL KETAL**

**[4,8-Dioxaspiro[2.5]oct-1-ene and 6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile,  
2-phenyl-]**



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## 1. Procedure

A. *2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane*.<sup>2</sup> A 100-mL, round-bottomed flask is equipped with a 10-mL Dean–Stark apparatus and a condenser. The flask is charged with 30.0 g (0.138 mol) of 1-bromo-3-chloro-2,2-dimethoxypropane (Note 1), 10.0 mL (0.138 mol) of 1,3-propanediol (Note 2), and 3 drops of concentrated sulfuric acid. The resulting solution is heated (bath temperature 140°C) for 8 hr (Note 3) with distillative removal of methanol (ca. 11 mL). The mixture is allowed to cool to room temperature and the crude product is partitioned in 150 mL of pentane and 40 mL of water. The organic phase is dried with magnesium sulfate and the solvent is removed under reduced pressure (Note 4). Distillation (1 mm, 90–95°C) yields 25.5–27.7 g (81–88%) of 2-(bromomethyl)-2-(chloromethyl)-1,3-dioxane, mp 57–59°C (Note 5).

B. *Cyclopropenone 1,3-propanediol ketal*.<sup>3</sup> A 1000-mL, three-necked, round-bottomed flask is equipped with a gas inlet, an acetone–dry ice condenser with a drying tube containing potassium hydroxide pellets, a stopper, and a magnetic stirring bar. The flask is placed in an acetone–dry ice bath and anhydrous ammonia (Note 6) is condensed into the flask (400 mL). A small piece of potassium metal (ca. 0.5 g) is added to the liquid ammonia and the cooling bath is removed. A catalytic amount of anhydrous ferric chloride (0.1 g) is added and the reaction mixture is allowed to warm to reflux temperature, at which time the deep blue color turns to gray. The remaining potassium metal (12.2 g, 0.31 g-atom total) is added in 0.5-g pieces over ca. 30 min. The reaction mixture is allowed to stir until a gray suspension results (20–30 min). A –50°C cooling bath is placed under the flask and the stopper is

replaced with a 125-mL, pressure-equalized dropping funnel containing 22.9 g (0.1 mol) of 2-(bromomethyl)-2-(chloromethyl)-1,3-dioxane in 50 mL of anhydrous ether. This solution is added dropwise to the solution of freshly generated potassium amide over 15 min while the temperature is maintained at  $-50^{\circ}\text{C}$  (Note 7). After the solution is stirred for 3 hr at  $-50^{\circ}$  to  $-60^{\circ}\text{C}$ , solid ammonium chloride is added slowly to quench the excess potassium amide (Note 8). The cooling bath is removed and the ammonia is allowed to evaporate. During the course of the evaporation, anhydrous ether (350 mL total) is added dropwise through the addition funnel to replace the ammonia. After the temperature has reached  $0^{\circ}\text{C}$ , the brown reaction mixture is filtered by suction through a coarse fritted-glass filter to remove the inorganic salts and the salts are washed twice with 25 mL of anhydrous ether. The combined ethereal filtrate and washes are concentrated under reduced pressure (80–100 mm,  $30^{\circ}\text{C}$ ) to constant weight (ca. 4–5 hr) (Note 9). The residue is transferred to a 50-mL, round-bottomed flask fitted with a water-cooled, short-path distillation head, and the product is distilled (1.25 mm;  $30\text{--}35^{\circ}\text{C}$ ) into an ice-cooled receiver. Cyclopropanone 1,3-propanediol ketal is obtained as a colorless liquid (6.1–7.8 g, 55–70% yield, (Note 10)).

C. 5,5-Dicyano-4-phenyl-2-cyclopenten-1-one 1,3-propanediol ketal. Benzylidenemalononitrile (Note 2) (3.85 g, 25 mmol) and cyclopropanone 1,3-propanediol ketal (5.6 g, mmol) are combined in 25 mL of dry distilled toluene (Note 11) in a sealed tube (Note 12) with a magnetic stirring bar. The reaction mixture is heated at  $80^{\circ}\text{C}$  for a 6.5 hr with stirring. The crude reaction mixture is filtered through a short plug of glass wool and applied to a Waters Associates Prep LC/System 500, eluting with 2.5 : 1 hexane/ethyl acetate (Note 13). The fractions containing product are combined and concentrated under reduced pressure to give 4–4.2 g (60–64%) of 5,5-dicyano-4-phenyl-2-cyclopenten-1-one 1,3-propanediol ketal as a white solid: mp  $139\text{--}141^{\circ}\text{C}$  (ethanol, (Note 14)).

## 2. Notes

1. The preparation<sup>4</sup> of this material has been described in detail: Breslow, R.; Pecoraro, J.; Sugimoto, T. *Org. Synth., Coll. Vol. VI* **1988**, 361.
2. The submitters employed material available from Aldrich Chemical Company, Inc. without further purification.
3. Shorter reaction times result in incomplete transketalization.
4. The checkers found that the product crystallizes, either on removal of solvent or in the condenser during the following distillation. To prevent the condensers tube becoming plugged by the crystalline product, an air-cooled, rather than a water-cooled, condenser jacket should be used.
5. The product has the following spectral properties:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.78 (m, 2 H,  $\text{CH}_2$ ), 3.70 (s, 2 H,  $\text{CH}_2\text{Cl}$ ), 3.80 (s, 2 H,  $\text{CH}_2\text{Br}$ ), 3.96 (t, 4 H,  $J = 6$ ,  $\text{OCH}_2$ ); IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 3030, 3000, 2900, 1485, 1430, 1245, 1202, 1158, 1135, 1105 (s), 1020.
6. Commercial anhydrous ammonia is employed without further drying.
7. Crystals that may form at the tip of the addition funnel are scraped off and allowed to drop into the reaction flask.
8. The checkers added a total of 25 g of solid ammonium chloride in portions of approximately 2 g with a spatula.
9. The checkers removed the solvent with a rotary evaporator at 20 mm and  $25^{\circ}\text{C}$ ; under these conditions only 1 hr is required to concentrate the solution to a constant weight.
10. This material should be stored under an argon atmosphere below  $0^{\circ}\text{C}$ . The product has the following spectral properties:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.83 (m, 2 H,  $\text{CH}_2$ ), 4.01 (t, 4 H,  $J = 6$ ,  $\text{OCH}_2$ ), 7.84 (s, 2 H,  $\text{CH}=\text{CH}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 25.4 ( $\text{CH}_2$ ), 65.6 ( $\text{OCH}_2$ ), 80.5 ( $\text{OCO}$ ), 125.1 ( $\text{C}=\text{C}$ ); IR (film)  $\text{cm}^{-1}$ : 3101, 2980, 2870, 1600, 1475, 1460, 1435, 1370, 1300, 1275, 1155, 1090, 1030, 935, 910, 865, 740.
11. Toluene was distilled from calcium hydride under a nitrogen atmosphere.
12. The resealable glass tube was fabricated from an Ace Glass medium-walled straight tube. The tube was permanently sealed on one end, and the other end remained internally threaded. The tube was sealed with a solid Teflon plug fitted with a FETFE O-ring. Various sizes of such tubes are now available from Ace Glass.
13. The submitters used medium pressure chromatography<sup>5</sup> on  $25 \times 1000$  mm of 230–400 mesh silica gel with a  $25 \times 250$ -mm scrubber column. The eluant (3 : 1 : 1 hexane : ethyl acetate : methylene chloride) was passed through the column at a rate of 15 mL/min, collecting 15-mL fractions. The checkers were unable to obtain pure product using a gravity column or flash chromatography.

14. The product has the following spectral properties:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.71 (dt, 1 H,  $J = 13.8$ ,  $J = 3.8$ ,  $\text{OCH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 2.1–2.3 (broad m, 1 H,  $\text{OCH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 3.9–4.3 (m, 4 H,  $\text{OCH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 4.63 (t, 1 H,  $J = 2.3$ , allylic CH), 6.25 (dd, 1 H,  $J = 6.3$ ,  $J = 2.0$ ,  $\text{CH}-\text{CH}=\text{CH}-\text{C}$ ), 6.62 (dd, 1 H,  $J = 6.3$ ,  $J = 2.6$ ,  $\text{CH}-\text{CH}=\text{CH}-\text{C}$ ), 7.3–7.5 (m, 5 H, phenyl); IR ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 3070, 2920, 2290 ( $\text{C}\equiv\text{N}$ ), 1510, 1465, 1350, 1260, 1210, 1175, 1140, 1100, 1080, 1040, 870, 705.

### 3. Discussion

Although a number of multistep procedures are available for the introduction of five-membered carbocycles, their direct formation in a thermal cycloaddition is rare.<sup>6</sup> Interest in the potential application of such a three-carbon + two-carbon **cyclopentane** cycloaddition has been derived from the expectation that such a process could prove to be an effective complement to the four-carbon + two-carbon Diels–Alder reaction, which is used extensively in the regio- and stereocontrolled preparation of functionalized six-membered carbocycles.

Cyclopropenone ketals, of which cyclopropenone 1,3-propanediol ketal (**1**) is a representative and unusually stable example, have proved to be useful equivalents of the 1,3-dipole (**i**) in a regiospecific three-carbon + two-carbon cycloaddition with electron-deficient olefins (Eq. 1). Table I shows representative results of a study of this reaction.<sup>7</sup>

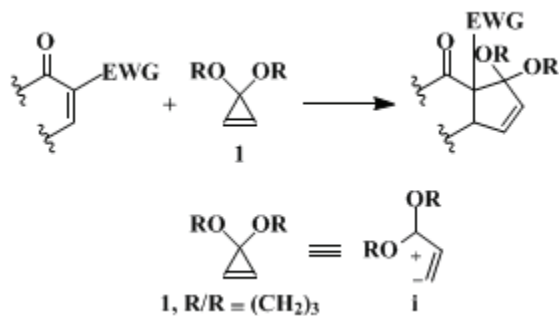
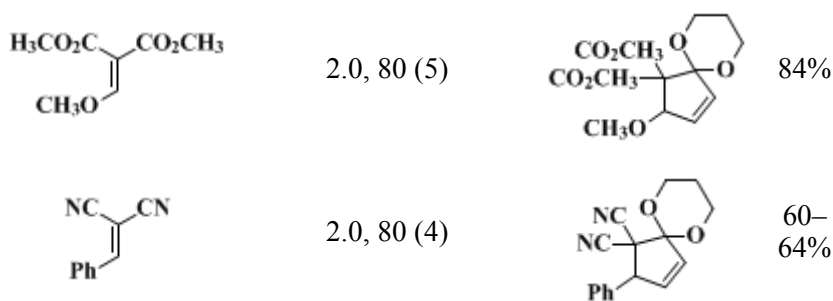


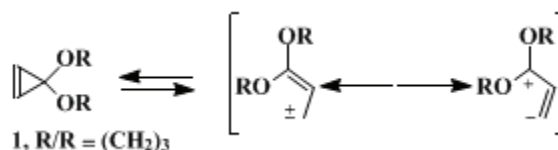
TABLE I  
REACTIONS OF CYCLOPROPENONE KETAL **1** WITH ELECTRON-DEFICIENT OLEFINS

Substrate	Conditions <sup>a</sup> equiv <b>1</b> , temp. °C(time hr)	Product	%Yield
	1.0–2.0, 80 (12)		42%
	1.0, 75 (13)		45%
	R = Et 1.5, 75 (13)		53%
	R = Me 2.5, 75 (32)		60%
	 CO <sub>2</sub> Et, CH <sub>3</sub>		1.5, 75 (15) 57%

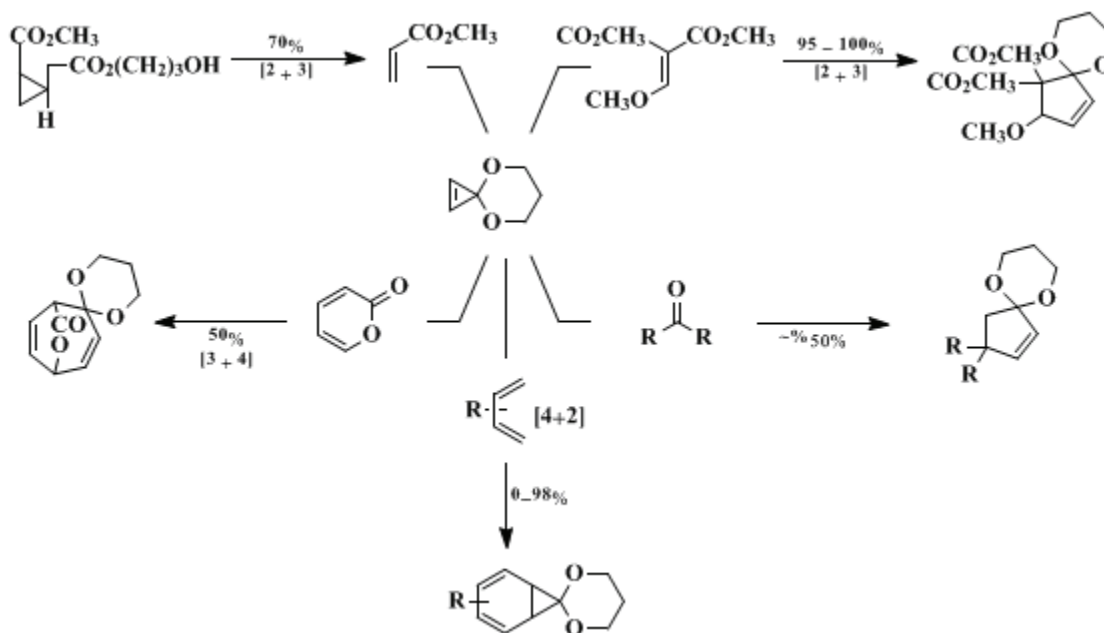


<sup>a</sup> All reactions were run in benzene (0.5–2.0 M in substrate) under nitrogen unless otherwise noted.

Studies have defined the scope of the thermal reactions of cyclopropanone ketals which are characterized by their thermal, reversible ring opening to provide reactive intermediates best represented as delocalized singlet vinyl carbenes, three-carbon 1,1-/1,3-dipoles without octet stabilization (Eq. 2).



In addition to the representative [3 + 2] cycloaddition reactions shown in Table I, the delocalized singlet vinyl carbenes have been shown to participate as  $\pi 2_s$  components of nonlinear cheletropic [ $\pi 2_s + \pi 2_a$ ] cycloadditions to provide cyclopropanes with an observable endo effect,<sup>8</sup> and as  $\pi 2_s$  components of [ $\pi 4_s + \pi 2_s$ ] cycloadditions with selected dienes to provide cycloheptadienes<sup>9,10</sup> (Scheme 1). This thermal reactivity of cyclopropanone ketals complements their dual participation as strained olefins in normal (HOMO<sub>diene</sub> controlled) and inverse electron demand (LUMO<sub>diene</sub> controlled) Diels–Alder reactions with electron-rich, electron-deficient, and neutral dienes under room temperature, thermal, and pressure-promoted Diels–Alder conditions.<sup>11,12,13</sup>



## References and Notes

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

Cyclopropenone 1,3-propanediol ketal

5,5-Dicyano-4-phenyl-2-cyclopenten-1-one 1,3-propanediol ketal

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

1,3-propanediol (504-63-2)

nitrogen (7727-37-9)

toluene (108-88-3)

ferric chloride (7705-08-0)

potassium (7440-09-7)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

potassium amide

hexane (110-54-3)

argon (7440-37-1)

1-Bromo-3-chloro-2,2-dimethoxypropane (22089-54-9)

calcium hydride (7789-78-8)

cyclopentane (287-92-3)

4,8-Dioxaspiro[2.5]oct-1-ene (60935-21-9)

6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl- (88442-12-0)

2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane (60935-30-0)

Benzylidenemalononitrile (2700-22-3)