



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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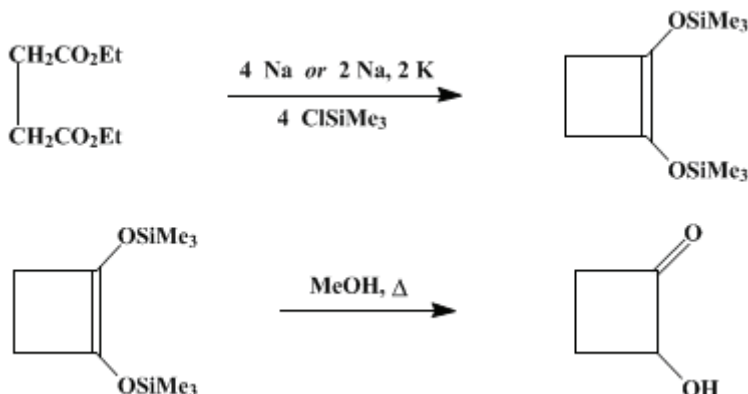
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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**ACYLOIN CONDENSATION IN WHICH
CHLOROTRIMETHYLSILANE IS USED AS A TRAPPING AGENT:
1,2-BIS(TRIMETHYLSILOXY)CYCLOBUTENE AND 2-
HYDROXYCYCLOBUTANONE**

[Trimethylsilane, 1-cyclobuten-1,2-ylenedioxybis- and Cyclobutanone, 2-hydroxy-]



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1. Procedure

Caution! See warnings concerning the use of impure chlorotrimethylsilane (Note 8) and finely dispersed alkali metals (Note 1), (Note 9), (Note 11) and (Note 19).

A. *1,2-Bis(trimethylsilyloxy)cyclobutene. Method 1.* A 1-l., three-necked, creased flask is fitted with a stirrer capable of forming a fine dispersion of molten sodium (Note 1), a reflux condenser, and a Hershberg addition funnel and maintained under an oxygen-free, nitrogen atmosphere. The flask is charged with 250–300 ml. of dry solvent (Note 2) and 9.6–9.8 g. (~0.4 g.-atom) of freshly cut sodium (Note 3), (Note 4). The solvent is brought to gentle reflux, and the stirrer is operated at full speed until the sodium is fully dispersed (Note 5). The stirrer speed is then reduced (Note 6), and a mixture of 17.4 g. (0.100 mole) of diethyl succinate (Note 7) and 45–50 g. (~0.4 mole) of chlorotrimethylsilane (Note 8) in 125 ml. of solvent is added over 1–3 hours. The reaction is exothermic, and a dark purple precipitate appears within a few minutes (Note 9). The solvent is maintained at reflux during and after the addition (Note 10). After five hours of additional stirring, the contents of the flask are cooled and filtered through a 75-mm., coarse sintered-disk funnel in a nitrogen dry-box (Note 11). The precipitate is washed several times with anhydrous diethyl ether or petroleum ether.

The colorless to pale yellow filtrate is transferred to a distilling flask, the solvent is evaporated, and the residue is distilled under reduced pressure (Note 12). After a small forerun (0.5–1.0 g.), 18 g. (78%) of the product is obtained at 82–86° (10 mm.) as a colorless liquid, n_D^{25} 1.4331 (Note 13).

Method 2. The apparatus described above is charged with 4.8–5.0 g. (~0.2 g.-atom) of clean sodium and 8.0–8.2 g. (~0.2 g.-atom) of clean potassium (Note 3), (Note 4). The flask is heated with a heat gun, forming the low-melting alloy, and 300–350 ml. of anhydrous ether is added from a freshly opened can. The stirrer is operated at full speed until the alloy is dispersed, then at a slower speed for the remainder of the reaction (Note 5), (Note 6). A mixture of 17.4 g. (0.100 mole) of diethylsuccinate (Note 7), 44 g. (0.41 mole) of chlorotrimethylsilane (Note 8), and 125 ml. of anhydrous ether is added at a rate sufficient to keep the reaction under control (Note 14). The purple mixture is stirred for another 4–6

hours (Note 9), then filtered and washed as above in a nitrogen dry-box (Note 11). The product is distilled as above, collecting a forerun, 0.5–2 g. to 80° (10 mm.), and then the product at 82–86° (10 mm.) as a colorless liquid, 13.8–16.1 g. (60–70%), n_D^{25} 1.4323–1.4330 (Note 15),(Note 16),(Note 17), (Note 18),(Note 19).

B. *2-Hydroxycyclobutanone*. A 1-l., three-necked flask fitted with a magnetic stirring bar, a sintered-disk gas-inlet tube, a dropping funnel, and a reflux condenser is charged with 450 ml. of reagent grade methanol (Note 20). Dry, oxygen-free nitrogen is bubbled vigorously through the methanol for about 1 hour before 23 g. (0.10 mole) of freshly distilled (Note 21) 1,2-bis(trimethylsilyloxy)cyclobutene is transferred under nitrogen to the addition funnel and added dropwise to the stirred methanol. Stirring under a reduced nitrogen flow is continued for 24–30 hours (Note 22). The methanol and methoxytrimethylsilane are removed under reduced pressure, and the residual 2-hydroxycyclobutanone is distilled through a short-path still as a colorless liquid, b.p. 52–57° (0.1 mm.), 6.1–7.4 g. (71–86%), n_D^{25} 1.4613–1.4685 (Note 23),(Note 24),(Note 25).

2. Notes

1. Generally a "Stir-O-Vac" stirrer (available from Labline Instruments, Inc., Melrose Park, Ill.) is used. A Vibromixer type of stirrer is also satisfactory, especially when high-dilution conditions are required. Both were used in the submitter's laboratory in conjunction with a short condenser surrounding the stirrer shaft to prevent loss of solvent or reactants. The condenser is required in high-dilution procedures with the Vibromixer to protect the diaphragm from solvent vapor. A plain sleeve stirrer with a Teflon paddle was used by the checkers, but the submitters warn that a Teflon paddle with highly dispersed metal, especially sodium-potassium alloy, is dangerous; explosions have been reported when Teflon and molten sodium are in contact. The submitters also emphasize that, because the large particle size can cause or lead to side reactions, a fine dispersion of metal is desirable, even with chlorotrimethylsilane.
2. Toluene is commonly used and can be dried with molecular sieves or directly distilled from calcium hydride into the reaction flask. Solvent stored over calcium hydride for several days is usually sufficiently dry to decant directly into the reaction flask, but distillation gives more consistent results. Any solvent with a boiling point sufficiently high to melt sodium is satisfactory. The submitters have also used methylcyclohexane and xylene in acyloin condensations. After the sodium is dispersed, the high-boiling solvent can be removed and replaced with anhydrous ether (as noted by the submitters) or can be retained and used in combination with ether (checkers).
3. The submitters routinely used a nitrogen dry-box to clean, cut, and weigh alkali metals. The checkers cut and weighed these metals under dry toluene.
4. An excess of metal is used because aromatic solvents are reduced to some extent, and it is easier than weighing out the exact amount.
5. One or two minutes of a "Stir-O-Vac" operated through a variable transformer at full voltage is required.
6. A setting of 30–40 volts on the variable transformer is used.
7. Diethyl succinate was obtained by the submitters from Eastman Organic Chemicals and used without purification. The checkers obtained the ester from British Drug Houses, Ltd., and distilled it at 100° (11 mm.). In general, it is preferable to distill or crystallize and dry all esters before attempting acyloin condensations.
8. Chlorotrimethylsilane, obtained from Eastman Organic Chemicals (submitters) and Aldrich Chemical Co. (checkers), was distilled from calcium hydride under nitrogen, then stored and weighed in a nitrogen dry-box. *Caution! It is particularly important that the chlorotrimethylsilane be distilled, preferably from calcium hydride, under nitrogen.* In at least one laboratory² the use of this reagent without prior purification led to explosions. Chlorotrimethylsilane may contain some dichlorodimethylsilane as an impurity, which hydrolyzes more readily than the monochlorosilane. Cautious treatment with a small amount of water, followed by distillation from calcium hydride, under nitrogen, removes this impurity. A further cautionary note concerning these reactions is also necessary. The explosions occurred in reactions run on a scale larger than 0.1 mole, using undistilled chlorotrimethylsilane and following a published procedure.³ This procedure requires mixing all the reagents at 20–30° and gradually warming the mixture. When this procedure was applied to diethyl pentanedioate on a large scale, the reaction became uncontrollably exothermic at about 50°.² It is recommended that the ester and chlorosilane be added together, dropwise, at a rate sufficient to maintain

the exothermic reaction. It is often unsafe with many esters to have a large amount of unreacted ester in the reaction mixture at any time.

9. The purple color seems to be indicative of a satisfactory reduction. When the color is light or no color develops, the yield is usually poor. Sometimes no reaction occurs. In this instance it is best to discard all residues (*pyrophoric*) carefully and start over with scrupulous attention to the dryness of all apparatus and reagents.

10. This is the usual procedure. The submitters report that equally good results are obtained if all the dispersing solvent is replaced by ether and the reaction is run at room temperature. The checkers have found a slightly modified procedure in which refluxing toluene (90 ml.) is used for dispersion, anhydrous ether (250 ml.) is added without removal of toluene, additional ether (120 ml.) is used for addition of diethyl succinate and chlorotrimethylsilane, and the mixture is heated under reflux for 14 hours, to be particularly convenient and to give consistently high yields (77–86%). The checkers have also found that prior removal of toluene does not affect the yields, but simplifies final purification. With toluene as solvent, better results are usually obtained at or near reflux. The amount of time following completion of addition of the ester is not critical. (It may vary with the compound being reduced.) The submitters generally use 4–6 hours or overnight, whichever happens to be more convenient.

11. Since a slight excess of metal is used, some may be left over. The excess chlorosilane and the product are sensitive to moisture. To avoid unpleasantness due to the pyrophoric nature of finely divided alkali metal residues, to hydrolysis of product, or production of free acid from the excess silane the submitters *always* filtered the reaction mixture in a nitrogen dry-box. The checkers used simple sintered-glass funnel filtration under a stream of dry nitrogen.

12. The submitters used a 250-mm. vacuum-jacketed Vigreux column fitted with a variable take-off head. Any good column should be as satisfactory.

13. The yield varies from 65 to 86%, n_D^{25} 1.4322–1.4338; b.p. 58–59° (2 mm.); 68–70° (6 mm.); 82–86° (10 mm.); 88–92° (13–14 mm.). In twelve separate runs (in toluene, toluene-ether, or in ether), the checkers did not obtain a yield below 76%.

14. The reaction is exothermic. Two hours is more than enough time. Too vigorous a reaction can be controlled with an acetone–dry ice bath.

15. The yields given are those obtained by the checkers. For this particular reaction the submitters have found the product to be cleaner and the yields higher (78–93%) with sodium-potassium reduction. This is not necessarily a general observation inasmuch as other reactions can occur with the alloy.⁴ The checkers found that a modification involving formation of the alloy in hot toluene (10 ml.), removal of most of the toluene with a stream of dry nitrogen, and dispersion of the alloy in ether led to somewhat better yields (81–85%). Because of convenience, safety, and yield reproducibility, they strongly favor Method 1.

16. The product can be examined for purity by ¹H NMR or by GC. The submitters have used XF-1150 columns successfully. Columns with polar sites will strip silyloxy groups from the bis(silyloxy) compounds and are unsatisfactory.

17. Both Methods 1 and 2 have been successfully applied to a wide range of 1,2-diesters⁵ and to a variety of other esters.⁶ The use of a high-dilution cycle permits this procedure to be applied to medium- and large-ring acyloins with good to excellent results.

18. The product is stable if stored in a tightly screw-capped bottle. Prolonged exposure to moist air leads to decomposition. The submitters have stored samples for several years with no change in physical properties.

19. *Caution! Disposal of residues must be made with care. When excess metal, especially sodium-potassium alloy, is used, the residues can be pyrophoric!*

20. The submitters used a freshly opened bottle for each hydrolysis.

21. Use of freshly distilled bis(silyloxy) compound is critical in many cases, especially in this example. The yield and, more particularly, the quality of the product deteriorate with the age of the sample. Traces of acid should be avoided because even as little as one drop of chlorotrimethylsilane added to the reaction mixture produces a different product. The longer the reaction time in the presence of acid, the greater is the number of other products formed.

22. The reaction time can be reduced considerably by gentle reflux. It is advantageous to follow the reaction by GC (see Note 16) if heating is used, because prolonged reflux can lead to side reactions.

23. The wide range of refractive indices is related to the time interval between distillation and measurement. The longer one waits, the higher the refractive index. This is apparently due to rapid

formation of dimer.

24. In the IR (CHCl_3), 2-hydroxycyclobutanone has a carbonyl band at 1780 cm^{-1} . Kept in nitrogen-filled screw-capped vials in the freezing compartment of a refrigerator, 2-hydroxycyclobutanone slowly but completely solidifies as its dimer. The IR spectrum (KBr) of the solid shows no carbonyl. However, a CHCl_3 solution of the solid does show the characteristic 1780 cm^{-1} band, indicating rapid equilibration with the monomer.

25. Air readily oxidizes 2-hydroxycyclobutanone; quantitative conversion to succinic acid occurs on standing in the open for several days.

3. Discussion

The discovery that chlorotrimethylsilane will react *in situ* with alcoholates and the acyloin enediolates^{3,7,8,9} provided the opportunity to prepare a wide range of four-membered acyloins for the first time.⁵ In addition, most acyloin reaction yields are improved, and some diesters, which were found to give Dieckmann condensation products as a result of the base formed concomitantly with the acyloin, can now be reductively cyclized in good yield.⁶ The general reaction conditions given for the cyclization of diethyl succinate have been applied to synthesis of four- to eight-membered rings with very good results.^{3,7,8,9} Likewise, when a high-dilution cycle is used, good to excellent cyclizations of eight- to fourteen-membered rings can be obtained. (Yields are 8, 72–85%; 9, 68%; 10, 58–69%; 11, 48%; 12, 68%; 13, 84%; 14, 67%.)¹⁰

For many reasons, use of the trapping agent is recommended as the most efficient method for running acyloin condensations. Among them are: (a) the work-up is very simple: filter and distill; (b) the bis(silyloxy)olefin is usually easier to store than the free acyloin and is readily purified by redistillation; (c) unwanted base-catalyzed side reactions during reduction are completely avoided; and (d) the bis(silyloxy)olefin can be easily converted directly into the diketone by treatment with 1 mole of bromine in carbon tetrachloride.^{11,12,13} Other reactions are described in Rühlmann's review and in *Organic Reactions*.¹⁴

Bis(silyloxy)cyclobutenes are also subject to a variety of special reactions. Probably the most interesting is the observation that they readily undergo a ring-opening reaction leading to butadiene derivatives⁵. This reaction has already been used to prepare largering diketones from cyclic 1,2-diesters¹⁵.

The synthesis of 2-hydroxycyclobutanone was chosen as a model for the use of a trapping agent because diethyl succinate is the most accessible of 1,2-diesters and the hydrolysis step for this compound is more difficult than most. Procedures developed for succinoin have been found broadly applicable in preparation of other sensitive acyloins.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 327
- Org. Syn. Coll. Vol. 7, 95
- Org. Syn. Coll. Vol. 7, 112
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

petroleum ether

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

Succinic acid (110-15-6)

toluene (108-88-3)

sodium (13966-32-0)

potassium (7440-09-7)

xylene (106-42-3)

methylcyclohexane (108-87-2)

Diethyl succinate (123-25-1)

sodium-potassium

calcium hydride (7789-78-8)

CHLOROTRIMETHYLSILANE (75-77-4)

1,2-bis(trimethylsilyloxy)cyclobutene,
Trimethylsilane, 1-cyclobuten-1,2-ylenedioxybis- (17082-61-0)

2-Hydroxycyclobutanone,
Cyclobutanone, 2-hydroxy- (17082-63-2)

diethylsuccinate

methoxytrimethylsilane (1825-61-2)

dichlorodimethylsilane (75-78-5)

monochlorosilane (13465-78-6)

diethyl pentanedioate (818-38-2)