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A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

VINYL RADICAL CYCLIZATION VIA ADDITION OF TIN RADICALS TO TRIPLE BONDS: 3-METHYLENE-4-ISOPROPYL-1,1-CYCLOPENTANEDICARBOXYLIC ACID, DIMETHYL ESTER

[1,1-Cyclopentanedicarboxylic acid, 3-methylene-4-(1-methylethyl)-, dimethyl ester]
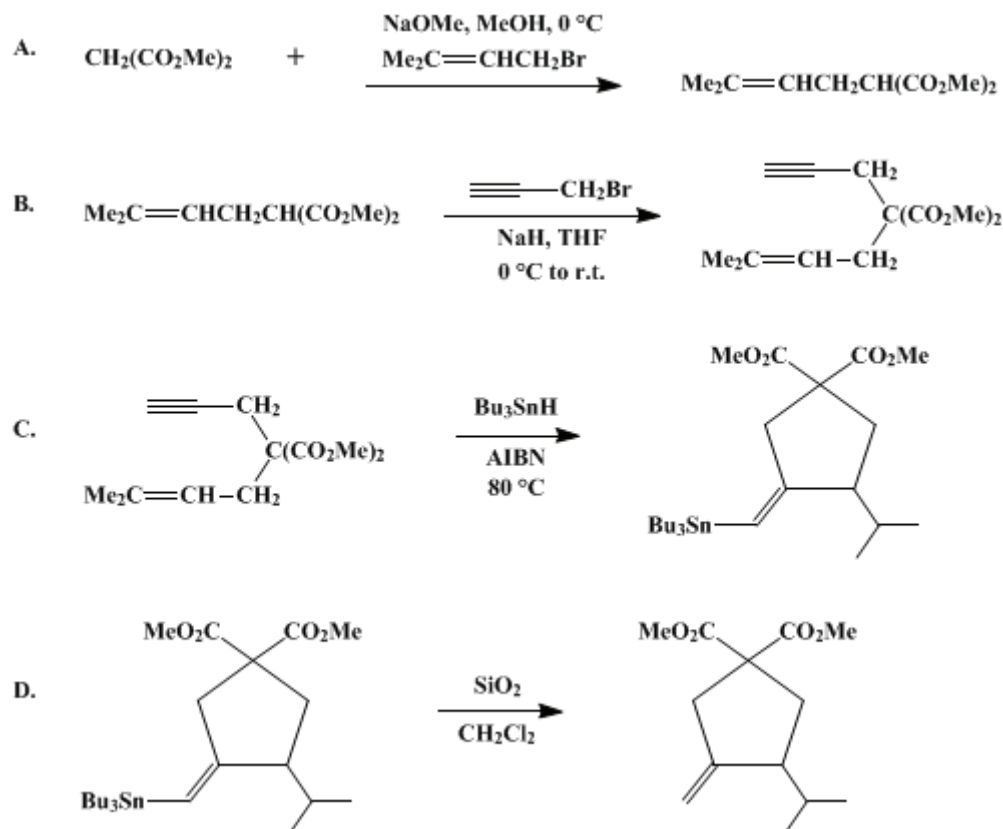
Submitted by Robert Mook, Jr. and Philip Michael Sher[1].
Checked by Anthony G. Schaefer and Leo A. Paquette.

1. Procedure

A. *(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester* **(1)**. To a 500-mL, flame-dried, three-necked, round-bottomed flask under an argon atmosphere and fitted with a thermometer, a pressure-equalizing addition funnel, and a magnetic stirring bar is added 250 mL of methanol (Note 1). The flask is immersed in an ice bath, and 6.7 g (0.29 mol) of sodium is added cautiously (Note 2). After the sodium has dissolved, the ice bath is removed, 36.9 g (0.28 mol) of dimethyl malonate (Note 1) is added at room temperature, and the solution is stirred for 0.5 hr. The reaction mixture is cooled to 0°C, and 45.8 g (0.31 mol) of 3,3-dimethylallyl bromide (Note 1) is added dropwise while the temperature is maintained near 5°C (Note 3). After 1 hr (Note 4), the reaction mixture is transferred to a 1-L, one-necked, round-bottomed flask with the aid of a small amount of methanol and concentrated with a rotary evaporator. The white residue is taken up in 400 mL of ether and 300 mL of a saturated salt/saturated sodium bicarbonate (1 : 1) solution and is transferred to a separatory funnel. The ether layer is separated, and the aqueous layer is extracted with ether (1 × 200 mL). The ether layers are combined, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. Distillation of the residue through a 6-in. Vigreux column (after a small forerun is collected) yields 43.9–44.5 g (78–79%) of **1**, bp 60–63°C (0.15 mm) (Note 5).

B. *(3-Methyl-2-butenyl)(2-propynyl)propanedioic acid, dimethyl ester* **(2)**. To a 1-L, flame-dried, three-necked, round-bottomed flask, equipped with a magnetic stirring bar (Note 6) and under an argon atmosphere, is added 9.0 g (0.19 mol) of sodium hydride dispersion (Note 7). The sodium hydride is washed with petroleum ether (4 × 30 mL), removing the petroleum ether by pipette after the sodium hydride has settled. The flask is then fitted with a thermometer and an over-dried pressure-equalizing addition funnel and charged with 500 mL of tetrahydrofuran (Note 7). The heterogenous mixture is cooled with an ice bath, and 36.4 g (0.18 mol) of the monoalkyl diester (1) is added dropwise at the rate of 1 drop/2–3 sec (Note 2). The cooling bath is removed when the addition is complete, and the solution is stirred until no more gas evolves (ca. 1 hr). The reaction mixture is recooled to 0°C, and 22 mL of propargyl bromide solution (0.20 mol) (Note 7) is added dropwise while the temperature is maintained at 0–10°C. Sodium bromide begins to precipitate within 20 min. The ice bath is removed, and the reaction mixture is stirred overnight (Note 8). After careful addition of 50 mL of water (Note 9) and removal of the stirring bar, the solution is transferred to a 1-L, one-necked, round-bottomed flask and concentrated with a rotary evaporator. The residue is taken up in 500 mL of ether and washed with water (3 × 300 mL) and saturated salt solution (1 × 100 mL). The aqueous layers are combined, saturated with salt, and extracted with ether (2 × 150 mL). The ether layers are combined, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue is distilled through a short-path distillation apparatus at 80°C (0.25 mm) to yield 34.0–34.2 g (79–80%) of (Note 10).

C. *(Z)-3-Tributylstannylmethylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester* **(3)**. A flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with argon, and 23.8 g (0.100 mol) of dialkylmalonate diester (2), 30.2 g (<0.104 mol) of tributyltin hydride (Note 11), and 40 mg (0.25 mmol) of azobisisobutyronitrile (AIBN) (Note 12) are added neat (Note 13) and (Note 14). The entire assembly is lowered into an oil bath maintained at 75–85°C, and the mixture is stirred. After an induction period of less than 30 min, an exothermic reaction occurs and produces a small amount of gas and a rise in the temperature of the oil bath (as much as 20°C for a small bath). After this point TLC shows that the reaction is essentially complete (Note 15)(Note 16)(Note 17). Unpurified 3 thus obtained is suitable for protodestannylation.

D. *3-Methylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester* **(4)**. Crude vinylstannane (3) is transferred to a 2-L Erlenmeyer flask containing 1 L of dichloromethane, 350 g of silica (Note 18), and a large (7 × 3-cm, egg-shaped) stirring bar. The flask is stoppered, and the mixture is stirred for 24–48 hr (Note 19). The mixture is divided into three portions. Each portion is filtered under reduced pressure with a 600-mL glass frit, and the silica is washed with ethyl acetate (8 × 200 mL) to extract all of the desired product (Note 20). The solution is filtered through Celite and the solvent is removed with a rotary evaporator. Distillation through a short-path distillation apparatus (with no forerun) gives 19.8–20.5 g of **4** (83–85% overall from **2**), bp 80°–85°C (0.2 mm) (Note 21).

2. Notes

1. The use of less solvent can result in gel formation. Methanol was freshly distilled from calcium hydride or magnesium metal. Dimethyl malonate (Aldrich Chemical Company, Inc.) was distilled before use. 3,3-Dimethyallyl bromide may be purchased from Aldrich Chemical Company, Inc. or Wiley Organics.
2. The apparatus should be vented. Hydrogen gas formation causes vigorous bubling.
3. At higher temperature more dialkylation occurs.
4. The reaction can be monitored by TLC eluting with 10% ethyl acetate/petroleum ether.
5. The physical properties are as follows: IR (neat) cm^{-1}: 2980, 1730–1760, 1435, 1040; ^{1}H 200 MHz NMR (CDCl$_3$) δ: 1.62 (s, 3 H), 1.65 (s, 3 H), 2.56 (t, 2 H, $J = 7$), 3.34 (t, 1 H, $J = 7$), 3.70 (s, 6 H), 5.06 (bt, 1 H, $J = 7$).
6. Unless a sufficiently large stirring bar is used the precipitate may be impossible to stir. An overhead mechanical stirrer can be substituted.
7. Sodium hydride, 50% oil dispersion, was purchased from Alfa Products, Morton/Thiokol, Inc. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Propargyl bromide (80% in toluene) was purchased from Aldrich Chemical Company, Inc. and used directly.
8. The reaction is generally complete sooner, but because it progress is difficult to monitor by TLC (since the starting material and product have similar R_f values) the submitters routinely allow more than

enough time.

9. Trace amounts of sodium hydride may still be present. If the water is added too quickly, a vigorous reaction results.

10. The checkers observed a boiling point of 99–100°C (0.35 mm) for this material. The physical properties are as follows: IR (neat) cm^{-1}: 3290, 2960, 1740, 1440; ^{1}H 300 MHz NMR (CDCl$_3$) δ: 1.61 (s, 3 H), 1.65 (s, 3 H), 1.97 (t, 1 H, J = 3), 2.7 (m, 4 H), 3.69 (s, 6 H), 4.9 (t, 1 H J = 7).

11. Tributyltin hydride 97%, was purchased from Aldrich Chemical Company, Inc. and used directly. A minimal excess of this reagent is desired in order to ensure clean distillation of 4. If the product is to be purified by chromatography, a 10% excess of tributyltin hydride can be used.

12. Azobisisobutyronitrile (AIBN) was purchased from Aldrich Chemical Company, Inc. and recrystallized from chloroform. To exclude the possibility of a violent reaction, no more than twice this amount should be used on this scale.

13. These reactions can also be run in benzene, which is preferable in cases where transfer of hydrogen to the vinyl radical is competitive with cyclization.

14. The submitters routinely interposed a Vigreux column between the reaction flask and the argon line to protect the argon line in the event of bumping.

15. The reaction mixture is routinely stirred hot for an additional 30 min to ensure complete conversion.

16. Vinylstannane (3) may protodestannylate on TLC, which could be confusing when monitoring Reaction C since dialkylmalonate diester (2) and protodestannylated product (4) have similar R_f values. The submitters found that TLC plates stored in the open air (as opposed to desiccator-stored plates) caused negligible protodestannylation.

17. Although vinylstannane 3 protodestannylates on silica, it may be isolated by flash chromatography in greater than 90% yield: IR (neat) cm^{-1}: 2960, 2930, 2880, 2860, 1740, 1615, 1465, 1435; ^{1}H 200 MHz NMR (CDCl$_3$) δ: 3.71 (s, 3 H), 3.73 (s, 3 H), 5.62 (bs, 1 H) with satellites.

18. The submitters employed Silica Woelm 32-63 purchased from Universal Scientific, Inc.; the checkers used Merck silica gel 60 (40–60 μm in size). Before use the silica was oven dried for several days at 160°C. Undried silica may be used, but larger quantities and/or longer reaction times are necessary.

19. TLC plates stored in the open air should be used (see (Note 16)) to monitor Reaction D accurately. Approximately 4% of noncyclized hydrostannylation product is produced in Reaction C. This material forms cospots with 3 (2.5% ethyl acetate in petroleum ether), but protodestannylates much more slowly. Therefore, by TLC Reaction D may appear not to go to completion.

20. A larger glass frit would obviate division of the mixture. In any case, the silica should be washed until by TLC the filtrate no longer contains 4.

21. The checkers observed a boiling point of 98–105°C (0.35 mm) for this product: IR (neat) cm^{-1}: 3080, 2960, 2875, 1735, 1655, 1435, 1385, 1365, 890. MS (CI) M + l = 241; ^{1}H 300 MHz NMR (CDCl$_3$) δ: 0.75 (d, 3 H, J = 7), 0.85 (d, 3 H, J = 7), 1.80 (m, 2 H), 2.40 (m, 2 H), 2.84 (m, 2 H), 3.64 (s, 3 H), 3.65 (s, 3 H), 4.72 (bs, 1 H), 4.90 (bs, 1 H).

3. Discussion

Free-radical reactions are proving to be synthetically useful alternatives for producing carbon–carbon bonds.[2] [3] [4] [5] [6] [7] [8] [9] [10,11] [12] [13] [14] [15] [16] [17] Recently, Stork has shown that vinyl radicals are valuable in ring forming reactions since they place a double bond in a predictable position.[11,12,13,14,15,16,17] Their compatibility with many unprotected functional groups and their ability to form quarternary centers are additional features which make vinyl radical cyclization an attractive synthetic method.

Previously, vinyl radicals for cyclization reactions were produced by the reduction of vinyl halides with tributyltin hydride. In the present procedure vinyl radicals are produced by the addition of tin radicals to triple bonds.[18] [19] These vinyl radicals undergo cyclization in an analogous fashion to those generated from vinyl halides. However, this approach provides vinylstannanes stereoselectively; these vinylstannanes may be utilized in a wide range of synthetic transformations.

Vinylstannanes[20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] are versatile synthetic intermediates. They serve as a source of stereospecific vinyl anions and vinyl cuprates.[20,23,32] [33] [34] In the presence of Pd(0), vinylstannanes can be acylated[35,36] or alkylated.[37,38] Epoxidation followed by rearrangement converts vinylstannanes into carbonyl compounds.[39] Treatment with halogens or N-halosuccinimides yields vinyl

halides.[20,21,22,23,34,40] Deuterium-labeled olefins result from deuterolysis of vinyl stannanes with AcOD or DCl.[23] Olefins identical to those produced in vinyl halide reductions are obtained on protodestannylation with silica gel, which, unlike simple acid treatment, solves the problem of separation from tin residues.[41]

Many examples of radicals kinetically favoring addition to double bonds over triple bonds are known.[42 43 44 45] Yet, vinyl radical cyclization in the present procedure is initiated by the addition of a tin radical to a triple bond.[46] The apparent selectivity of the tin radical for the triple bond in the presence of a double bond is, at least in some cases, a result of reversible addition to both followed by selective cyclization of the vinyl radical.[18,19]

References and Notes

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46. The sterically less biased case of allylpropargyl malonate gives greater than 75% of analogous product.

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

petroleum ether

silica

3,3-Dimethyallyl bromide

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

sodium bromide (7647-15-6)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

argon (7440-37-1)

tributyltin hydride (688-73-3)

calcium hydride (7789-78-8)

propargyl bromide (106-96-7)

dimethyl malonate (108-59-8)

3-Methylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester,
1,1-Cyclopentanedicarboxylic acid, 3-methylene-4-(1-methylethyl)-, dimethyl ester (107473-16-5)

3,3-dimethylallyl bromide (870-63-3)

azobisisobutyronitrile (78-67-1)

(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester (43219-18-7)

(3-Methyl-2-butenyl)(2-propynyl)propanedioic acid, dimethyl ester (107473-14-3)

(Z)-3-Tributylstannylmethylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester