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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.

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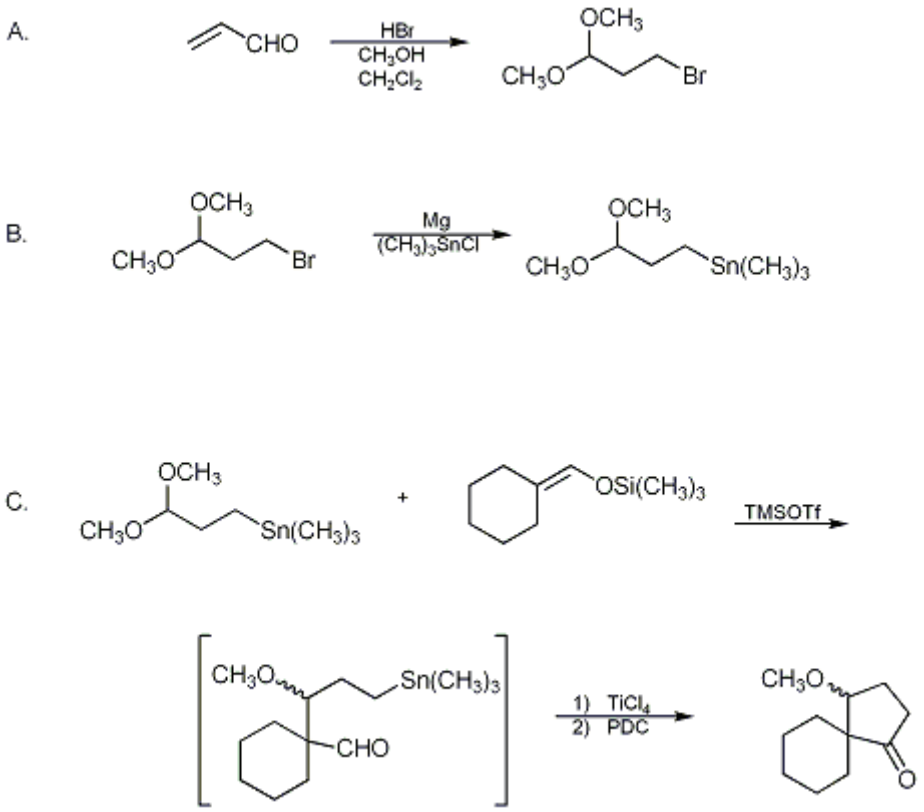
SPIROANNELATION OF ENOL SILANES: 2-OXO-5-METHOXYSPIRO[5.4]DECANE

[Spiro[4.5]decan-1-one, 4-methoxy-]



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1. Procedure

CAUTION! Many organotin compounds are known to be highly toxic[3] (Note 1), and hydrogen bromide (HBr), titanium tetrachloride ($TiCl_4$), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) are corrosive. Steps A-C should be performed in an efficient fume hood while wearlng gloves and adequate eye protection.

A. *1-Bromo-3,3-dimethoxypropane*(Note 2). Into a flame-dried, tared, 1-L, round-bottomed flask containing 500 mL of methylene chloride (CH_2Cl_2) (Note 3) at 0°C is bubbled anhydrous hydrogen bromide for approximately 15 min (33.0 g, 0.408 mol of HBr absorbed) (Note 4),(Note 5). Acrolein (22.9 g, 27.2 mL, 0.408 mol) is added rapidly (30 sec) via syringe to the stirred solution (Note 6). After 2 min, a solution of 86.6 g (89.3 mL, 0.816 mol) of trimethyl orthoformate (Note 7) in methanol (100 mL) is introduced into the reaction mixture via cannula over 5 min. The reaction mixture is stirred for 10 min at 0°C, and solid anhydrous calcium carbonate (12.0 g, 0.120 mol) is then added in one portion. The reaction mixture is stirred for an additional 1 hr, the solution is filtered, and the filtrate concentrated under reduced pressure to ca. 50 mL. The residue is distilled through a 25-cm Vigreux column under reduced pressure to give, after a forerun of variable amount (~10 mL) (Note 8), 38.8 g (52%) of 1-bromo-3,3-dimethoxypropane as a colorless liquid, bp 67–69°C at 24 mm (Note 9).

B. *1-Trimethylstannyl-3,3-dimethoxypropane*. An oven-dried, 500-mL, three-necked, round-bottomed flask fitted with a reflux condenser, nitrogen inlet tube, pressure-equalizing addition funnel, and rubber septum is charged with magnesium turnings (1.34 g, 55.2 mmol). The apparatus is carefully flame-dried under a flow of nitrogen and allowed to cool to room temperature. Tetrahydrofuran (5 mL) (Note 10) is added to the flask and a solution of 1-bromo-3,3-dimethoxypropane (10.10 g, 55.2 mmol) in tetrahydrofuran (10 mL) is added to the dropping funnel. A small portion (0.5 mL) of the solution of 1-bromo-3,3-dimethoxypropane is added to the flask along with 3 drops of 1,2-dibromoethane, with warming (Note 11), until reaction commences. Stirring is begun and the remainder of the bromide solution is added dropwise to the reaction mixture. After ca. 5 min the reaction becomes vigorous and a further 35 mL of tetrahydrofuran is added via a syringe. The reaction is allowed to stir at room temperature for 1 hr after addition is complete, by which time all the magnesium has been consumed. A solution of chlorotrimethylstannane (11.0 g, 55.2 mmol) (Note 12) in tetrahydrofuran (50 mL) is then added rapidly to the reaction mixture which is allowed to stir for 18 hr at room temperature before being poured into water (100 mL). The aqueous phase is washed with diethyl ether (3 × 100 mL), the combined organic phases are dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure to afford a yellow liquid (14.18 g).

The crude product is dissolved in petroleum ether (10 mL) (Note 13) and poured onto a column (45-mm diameter) filled with 350 g of silica gel (Merck 230–400 mesh) for flash chromatography. Elution under pressure (Note 14), initially with 2% diethyl ether in petroleum ether (Note 15) and then with increasing amounts of diethyl ether (up to 10%) in petroleum ether, gives, after removal of the solvent under reduced pressure, 1-trimethylstannyl-3,3-dimethoxypropane as a colorless liquid (11.9 g; 81%).

C. *2-Oxo-5-methoxyspiro[5.4]decane*. An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, nitrogen inlet tube, pressure-equalizing dropping funnel, and a rubber septum, and allowed to cool under a flow of dry nitrogen. The flask is charged with 1-trimethylstannyl-3,3-dimethoxypropane (8.69 g, 32.6 mmol), [(1-trimethylsilyloxy)methylene] cyclohexane (6.0 g, 32.6 mmol) (Note 16) and dichloromethane (100 mL) (Note 17). The mixture is stirred and cooled to −78°C using an acetone-dry ice bath, and trimethylsilyl trifluoromethanesulfonate (1.47 g; 6.6 mmol) (Note 18) is added dropwise. After 1.5 hr all starting materials have been consumed (Note 19), and a solution of titanium tetrachloride (7.40 g, 39.0 mmol) (Note 20) in dichloromethane (10 mL) is added dropwise at −78°C with stirring. On completion of the reaction, which requires 2 hr (Note 19), dichloromethane (250 mL) is added slowly so that the temperature does not rise above −70° C. Pyridinium dichromate (PDC) (20.32 g, 54.0 mmol) (Note 21) is added in 2-g portions. Stirring is then continued overnight while the reaction is allowed to warm to room temperature. Sodium-dried diethyl ether (300 mL) is added and the reaction mixture filtered through a short column of Celite. The solid residues are washed thoroughly with diethyl ether (5 × 50 mL), and the combined filtrates are concentrated under reduced pressure (Note 22), redissolved in diethyl ether, washed with 10% aqueous HCI (1 × 100 mL), brine (1 × 100 mL), saturated aqueous sodium hydrogen carbonate solution (1 × 100 mL), dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure to afford a yellow liquid (8.20 g).

The crude product is dissolved in diethyl ether/petroleum ether (1:5) (5 mL) and poured onto a column (45-mm diameter) filled with 200 g of silica gel (Merck 230–400 mesh for flash chromatography). Elution (Note 23) under pressure (Note 14) with diethyl ether/petroleum ether (1:5) gives 2-oxo-5-methoxyspiro[5.4]decane as a colorless liquid (4.43 g; 75%) (Note 24).

2. Notes

1. *Because of the highly toxic nature of many tin compounds all tin residues from these reactions, including those extracted by aqueous washing, were collected together by the submitters and dispatched to a licensed chemical waste disposal unit for burning in a chemical incinerator, equipped with an afterburner and scrubbers.*
2. This procedure is essentially that of Battersby and co-workers.[4]
3. Reagent grade methylene chloride was distilled from calcium hydride (CaH_2) prior to use.
4. A steady stream of HBr was introduced via a Pasteur pipette with the tip extending into the solution.
5. The solution is almost saturated after 15 min as judged by evolution of HBr.

6. Acrolein was obtained from the Aldrich Chemical Company, Inc., and distilled before use.
7. Trimethyl orthoformate was obtained from the Aldrich Chemical Company, Inc., and used as received.
8. The forerun consists primarily of methanol and trimethyl orthoformate.
9. The checkers found that commercially available 3-bromo-1,1-dimethoxypropane (Aldrich Chemical Company, Inc.) was unsatisfactory, even after purification, for preparation of the stannane in part B, resulting in greatly diminished yields.
10. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone ketyl radical immediately prior to use.
11. Warming was achieved by use of a water bath at 40°C.
12. Chlorotrimethylstannane was obtained from the Aldrich Chemical Company, Inc. and was used without further purification.
13. Petroleum ether boiling at 40–60°C was distilled immediately prior to use.
14. The submitters used a compressed air line at a pressure that maintained a flow rate of 5 mL min^{-1}.
15. Preliminary elution allows removal of hexamethyldistannoxane, formed as a by-product in the reaction, which slowly precipitates from the elution solvent as a white solid. A total of 1200 mL of solvent was collected in 30-mL fractions.
16. [(1-Trimethylsilyloxy)methylene]cyclohexane was prepared from the corresponding carboxaldehyde according to the method of House.[5] [6] Cyclohexane carboxaldehyde was obtained from the Aldrich Chemical Company, Inc., and purified by distillation at atmospheric pressure (bp 160–164°C).
17. Dichloromethane was distilled from CaH_2 immediately prior to use.
18. Trimethylsilyl trifluoromethanesulfonate was obtained from the Aldrich Chemical Company, Inc., and was purified by distillation under nitrogen (bp 142°C/760 mm), immediately prior to use.
19. The progress of the reaction is conveniently monitored by TLC on Kieselgel 60 F_{254} eluting, for the first bond-forming reaction, with diethyl ether:petroleum ether (1:9). The intermediate aldehyde had an R_f of 0.5, and the starting acetal an R_f = 0.45. The second bond-forming reaction was monitored by elution with diethyl ether:petroleum ether (2:3), and the R_f of the product was 0.4.
20. Titanium tetrachloride was obtained from the Aldrich Chemical Company, Inc., and was purified by distillation under nitrogen (bp 136°C/700 mm) immediately prior to use.
21. Pyridinium dichromate was prepared by the method of Corey.[7] The checkers employed PDC, obtained from the Aldrich Chemical Company, Inc., that was used as received.
22. This evaporation removes dichloromethane used in the original reaction, and assists isolation of the product.
23. A total of 600 mL of solvent was collected in 30-mL fractions.
24. The purity of the product was found to be 97% by high-field NMR (270 MHz). Physical properties are as follows: Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%. Found: C, 72.60; H, 9.94%. ν_{max} 1720 (C=O), 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.2–1.8 (10 H, m, CH_2), 1.81–2.40 (4 H, m, CH_2), 3.38 (3 H, s, OCH_3), 3.78 (1 H, m, CH-OCH_3); ^{13}C NMR ($CDCl_3$) δ: 22.13, 22.40, 22.77, 25.64, 25.94, 31.25, 34.12 (all t, CH_2), 54.11 (s, quat C), 56.92 (q, OCH_3), 83.87 (d, C-OCH_3), 221.30; m/z 182 (M^+).

Waste Disposal Information

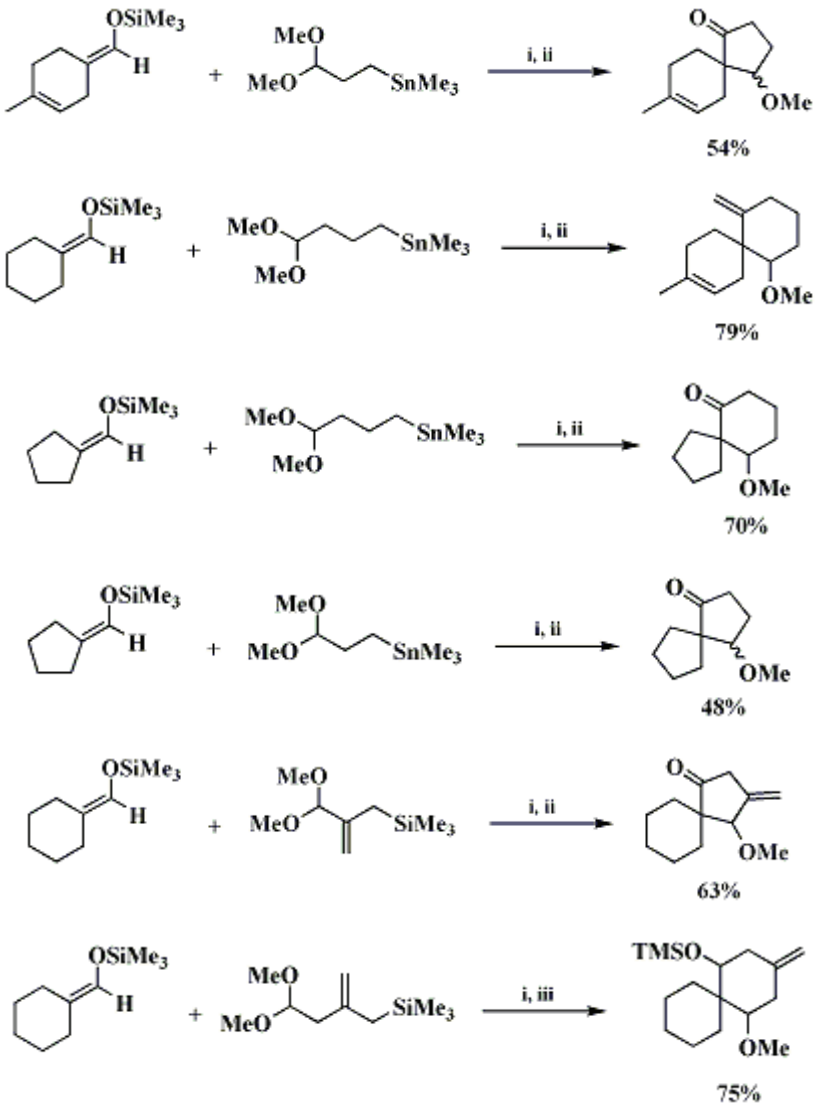
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. See (Note 1).

3. Discussion

The synthesis of spirocyclic compounds and quaternary carbon centers in general has been an area of intense synthetic activity,[8] because of the widespread occurrence of such products in nature, and because of the challenge they present to synthetic methodology. The reaction described here is a very simple method for constructing such systems in a single step, a two-bond forming, annelation process, using readily available starting materials. This new process involves the chemoselective[9] *intermolecular* reaction of the acetal function of a bifunctional alkyl stannane or allyl silane with an enol silane, followed by *intramolecular* ring closure to give an annelated product. By using a range of bifunctional reagents of this type, a highly efficient single-step construction of fused five-,[10,11] six-,[12] seven-,[12] eight-,[13] and nine-membered rings,[13] and of five-, six-, and seven-membered spirocyclic ring systems has been developed.[14,15]

The new spiroannelation method gives, by use of both the tin and silicon chemistry, ready access to [4.4], [4.5], [5.5], [4.6], and [5.6] spirocyclic systems as well as five-, six-, and seven-membered rings possessing a quaternary center. An in situ oxidation, or protection of an initially formed crude secondary alcohol increases the ease of isolation of the product and leads to improved overall yields. Furthermore, for symmetrical substrates, this chemodifferentiates two oxygen functionalities at equivalent carbon atoms. This makes the reaction potentially stereoconvergent at the newly formed quaternary center (see Table).

TABLE
SPIROCYCLIC COMPOUNDS



i. TMSOTf - $TiCl_4$; ii. PDC; iii. TMSOTMS/DMAP

Probably the best alternative to the present procedure, in terms of generality, is the use of a cycloaddition strategy that can give access to a wide range of different sized spirocyclic molecules.[16]

References and Notes

1. This work was carried out at the School of Chemistry, The University. Bristol, BS8 1TS, England, (*Thomas V. Lee is deceased);

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

petroleum ether

benzophenone ketyl

brine

2-OXO-5-METHOXYSPlRO[5.4]DECANE

Sodium-dried diethyl ether

methanol (67-56-1)

diethyl ether (60-29-7)

Acrolein (107-02-8)

sodium hydrogen carbonate (144-55-8)

magnesium,
magnesium turnings (7439-95-4)

hydrogen bromide,
HBr (10035-10-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

tin (7440-31-5)

calcium carbonate (471-34-1)

carbon (7782-42-5)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

methylene chloride,
dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

titanium tetrachloride (7550-45-0)

Cyclohexane carboxaldehyde (2043-61-0)

calcium hydride (7789-78-8)

silicon

pyridinium dichromate (20039-37-6)

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

trimethyl orthoformate (149-73-5)

chlorotrimethylstannane (1066-45-1)

Spiro[4.5]decan-1-one, 4-methoxy- (108264-15-9)

1-Bromo-3,3-dimethoxypropane,
3-bromo-1,1-dimethoxypropane (36255-44-4)

1-Trimethylstannyl-3,3-dimethoxypropane (102402-80-2)

2-Oxo-5-methoxyspiro[5.4]decane

hexamethyldistannoxane

[(1-Trimethylsilyloxy)methylene]cyclohexane