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AN EFFICIENT SYNTHESIS OF 2-TRIMETHYLSILYL-2-PROPENAL, A USEFUL THREE-CARBON SYNTHON

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Abstract: A formal efficient synthesis of 2-trimethylsilyl-2-propenal (**2**), a potentially useful synthetic reagent, is hereby described. The readily available α-bromovinyltrimethylsilane can be converted into 2-trimethylsilyl-2-propen-1-ol (**1**) via Grignard formation followed by addition of paraformaldehyde. The alcohol **1** can be oxidized using Jones reagent or PCC to yield the desired aldehyde **2**.

In our research directed toward natural product syntheses, we needed to use 2-trimethylsilyl-2-propenal (**2**), a simple three-carbon organic synthon. However, no direct approach was found in the literature for synthesizing the aldehyde **2**. Although there are indirect approaches[1-4] (see **Scheme II**), they are rather long and laborious for making this simple molecule. Hence, we found an alternative which provided improved efficiency in synthesizing 2-trimethylsilyl-2-propenal with excellent purity in large quantities.

In **Scheme I** (our approach), α-bromovinyltrimethylsilane was conveniently converted to the corresponding Grignard reagent, and the addition of paraformaldehyde provided the alcohol **1** in 65-73% yield. The alcohol **1** was then oxidized via Jones Oxidation or PCC to furnish 2-trimethylsilyl-2-propenal (**2**) in 45-60% yield. Reactions could be carried out in large scale (0.1 mol) and products could be easily isolated using common aqueous/organic workups and purified through distillation under reduced pressures.

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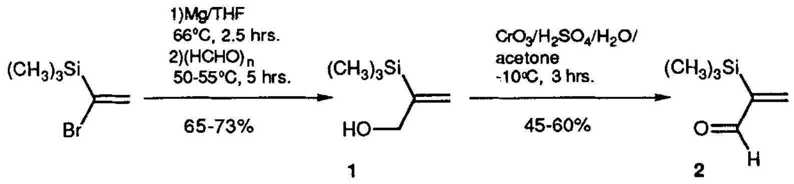
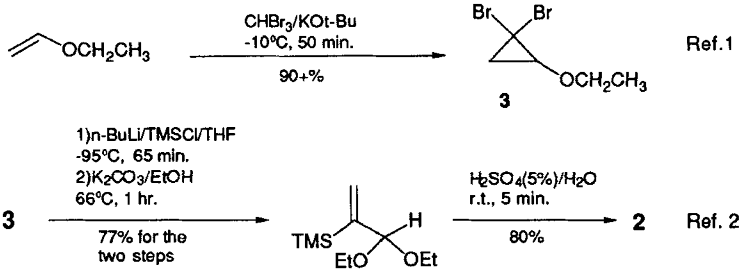
Scheme I

Our Approach

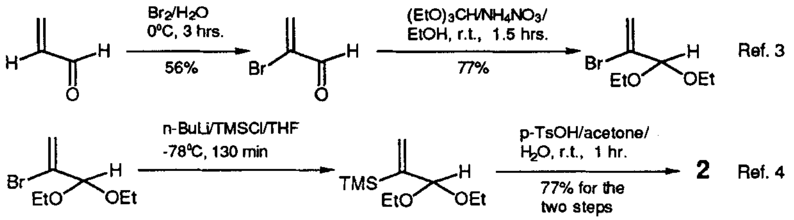


Scheme II

Indirect Syntheses of 2



Approach I



Approach II

Our procedure presents a simple and direct synthesis of 2-trimethylsilyl-2-propenal (**2**). It is an improvement in comparison with existing indirect procedures (**Scheme II**) in terms of the number of steps, scales and the overall yield.[1-4] The aldehyde **2** is a three-carbon synthon that has a variety of potential utilities. It already has been used extensively in studying the effect of the silyl group on the olefin in a series of reactions.[5,6] **2** is also an important intermediate in synthesis of

3-trimethylsilyl-3-buten-2-one,[4] and the α-silylated vinyl ketones are crucial intermediates in syntheses of fused polycyclic systems.[7] Furthermore, the aldehyde **2** is itself a useful three-carbon Michael acceptor in organic syntheses, and can be further transformed into acetals or thioacetals which are used as masked aldehydes or acyl carbanions.[8]

Experimental Procedures

All chemicals including solvents were purchased from the Aldrich Chemical Company, Inc. All reactions were performed under the nitrogen atmosphere. THF was dried over Na/benzophenone ketyl and distilled under nitrogen. All distillations were carried out using Cenco Hyvac Mechanical Vacuum Pump equipped with Ace Glass McLeod Vacuum Gauge. IR spectra were obtained on a Nicolet Instrument Corporation 20 SXB FT-IR spectrometer. ^{1}H NMR spectra were recorded at 500 MHz on a Chicago DS-1000 spectrometer interfaced with a Nicolet Instrument Corporation series 1280 data acquisition system. Chemical shifts (δ) were reported as parts per million (ppm) downfield from tetramethylsilane (TMS) which was used as an internal reference. Analytical TLC was performed by using 0.25mm EM Science (Merck) silica gel plates with F-254 as the indicator. Visualization was accomplished by UV light and potassium permanganate staining solution.[14]

2-Trimethylsilyl-2-propen-1-ol (1):

A flame-dried 500-mL round-bottom flask, equipped with a refluxing condenser, a pressure-equalized dropping funnel, and a magnetic stirring bar, was charged with freshly grounded Mg (4.37 g, 0.180 mol), I_2 (2 crystals), and anhydrous THF (100 mL). A solution of α-bromovinyltrimethylsilane (26.8 g, 0.150 mol)[9] in THF (120 mL) was placed in the dropping funnel. Initially the bromide solution was added dropwise to the vigorously stirred magnesium suspension while a flame was applied for 30 secs. to ignite the Grignard formation. Once the Grignard had started, the addition of the bromide solution was at a rate that maintained a gentle reflux of THF (needed 30 mins.). After completing the addition, the homogeneous Grignard solution was refluxed for 2.5 hrs. The light yellow solution was then cooled to 30 ^{o}C and 2,2'-bipyridyl (5 mg) was added as an indicator, giving a maroon red Grignard solution.[10] Dried paraformaldehyde (4.73 g, 0.158 mol)[11] was introduced at this time to the Grignard in one shot. After the initial exothermicity had subsided, the heterogeneous mixture was stirred at 50-55 °C for 5 hrs. The gradual disappearing of the red color (turning back to pale yellow) and regaining of the homogeneity indicated the completion of the reaction. The reaction was quenched dropwise carefully (exothermic quenching) with sat. NH_4Cl (25 mL) and the resulting mixture was then filtered. The filter cake was washed with sat. NaCl (100 mL) and ether (100 mL), and the filtrate was poured into sat. NaCl (150 mL) overlaid with ether (150 mL). The aqueous layer was again extracted with ether (2 x 100 mL). The combined ether extracts were washed with sat. NaCl (250 mL), dried (Na_2SO_4) and evaporated under the reduced pressure to give a dark yellow oil (18.2 g). Distillation (79-80 °C at 55 mm Hg) (lit.[12] b.p. 74-75 °C at 30 mm Hg) of the crude oil afforded the pure alcohol **1** as a pale yellow oil; yield: 12.6-14.2 g (65-73%).

IR (neat): υ = 3346 (brd., -O-H), 2956 (sp^3 -C-H), 1249 (-C-O), 759 (-C-Si) cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ = 0.12 (s, 9H, $(CH_3)_3Si$-), 4.26 (d, J=1.2 Hz, 2H, -CH_2OH), 5.42 (brs, 1H, terminal vinyl), 5.78 (brs, 1H, terminal vinyl).

2-Trimethylsilyl-2-propenal (2):

The alcohol **1** prepared above (15.5 g, 0.119 mol) was dissolved in reagent grade acetone (100 mL) at -10 °C (ice/acetone bath) in a 250-mL round-bottom flask. At first 1.8 M Jones reagent (10 mL)[13] was added carefully dropwise via a Pasteur pipet to the cold alcohol solution. Then the rest of the Jones reagent (75 mL) was cautiously added in 10-mL portions to the alcohol mixture. After the addition was completed, the reaction mixture was stirred at -10 °C for 3.0 hrs and monitored closely via TLC analysis (10%EtOAc in Pet. Ether, 0.25 mm silica gel plates, and $KMnO_4$ staining solution[14]). At the end of the reaction, 2-propanol (2.5 mL) was added to quench the excess oxidant. After stirring for 15 mins., the reaction mixture was poured into sat. NaCl (250 mL) overlaid with ether (250 mL). The aqueous layer was again extracted with ether (2 x 100 mL). The combined ether extracts were washed with sat. NaCl (250 mL), dried (Na_2SO_4) and carefully evaporated (**2** is quite volatile) under the reduced pressure (>80mmHg) at low temperatures (<20°C) to provide a yellow oil (12.6 g). Distillation (50 °C at 35 mm Hg) (lit.[5] b.p. 60-69 °C at 120 mm Hg) of the crude material gave the clean aldehyde **2** as a colorless oil; yield: 6.8-9.1 g (45-60%).

IR (neat): υ = 2957 (sp^3 -C-H), 2857 (aldehyde (C=O)-H), 1700 (conjugated aldehyde -(C=O)), 1249 (-C-O), 840 (-C-Si) cm^{-1}.
^1H-NMR ($CDCl_3$): δ = 0.18 (s, 9H, $(CH_3)_3Si$-), 6.62 (d, J=2.1 Hz, 1H, terminal vinyl), 6.69 (d, J=2.0 Hz, 1H, terminal vinyl), 9.64 (s, 1H, -CHO).

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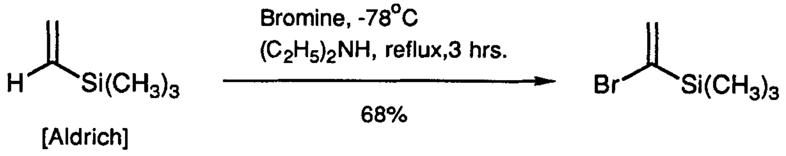
(9) (a) α-Bromovinyltrimethylsilane can be either purchased from Aldrich Chemical Company at $12.80 per gram or readily synthesized from vinyltrimethylsilane.[9b] (b) Boeckman, R. K., Jr.; Blum, D. M.; Ganem, B.; Haley, N. *Organic Syn. Coll. Vol. VI.* **1988**, 1033.



Starting scale: 90.0g(0.9mol)

(10) (a) The reagent 2,2'-bipyridyl, available from the Aldrich Chemical Company, Inc., appears red in solutions containing organolithium and organomagnesium reagents and is thereby an excellent indicator.[10b] Its use here allows us to detect the relative extent of the reaction. (b) Smith, A. B., III; Branca, S. J.; Guaciao, M. A.; Wovkulich, P. M.; Korn, A. *Organic Syn.* **1983**, *61*, 65, and the references therein.

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(14) The $KMnO_4$ staining solution is made from dissolving $KMnO_4$ (3.00 g) in a solution of K_2CO_3 (20.0 g) and 5% $NaOH_{(aq)}$ (5.00 mL) in H_2O (300 mL). Rf value for the alcohol **1** is 0.34, and 0.68 for the aldehyde **2** in 10% EtOAc/PE eluting medium.

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