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A CONVENIENT SYNTHESIS OF β-(TRIMETHYLSILYL)ETHANOL[†]

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Summary: A novel, simple and high yield synthesis of β-(trimethylsilyl)ethanol in pure form is reported.

Although β-TMS ethanol has proven to be an excellent reagent for the protection of carboxyl[1], amino[2], and hydroxyl[3] groups and recently for the anomeric center in carbohydrates[4], its use has not been widespread. The high cost of this reagent[5] has not encouraged its use. Furthermore, there is no procedure[6] reported from which β-TMS ethanol can be prepared in pure form and in good yield from relatively inexpensive materials. This paper now reports a simple, high yield and economical preparation of the silyl reagent in pure form.

β-TMS ethanol can be prepared on a convenient scale[7] as follows: A 250-ml two-necked flask equipped with a water cooled condenser (fitted with a three-way stopcock to serve as a nitrogen gas inlet-outlet) was charged with magnesium (3.96 g) and α-(chloromethyl)-trimethylsilane[8] (20 g, 163 mmol) in 90 ml anhydrous ether. The Grignard reaction was initiated by gentle heating (a heat gun is very convenient). The reaction is very highly exothermic and cooling in an ice-water bath was necessary to maintain gentle reflux. When all the magnesium had dissolved paraformaldehyde (5 g) was added. The mixture was refluxed vigorously for about 15 min followed by gentle reflux for about 2 h. The cooled reaction mixture was diluted with more ether and hydrolyzed with saturated ammonium chloride. The aqueous layer was extracted several times with ether and the combined ethereal fractions were dried over sodium sulfate. Evaporation (*in vacuo*) gave a yellow free flowing oil (approx. 20 g, 104% based on α-(chloromethyl)trimethylsilane).

Distillation afforded 18.4 g (approx. 96%) of pure, colorless β-TMS ethanol; b.p. 34-35°/1.5 mm, Lit.[1b] 50-52°/10 mm.

The crude mixture was analyzed by GC/MS and the results are shown in Table I.

The side products that are formed are inert under the conditions required to introduce β-TMS ethanol as a protecting group and hence cause no problem if the crude mixture is used. Nevertheless, if pure reagent is absolutely necessary, it is possible to obtain it by a simple distillation.

[†] β-TMS ethanol.

Table I. GC*/MS Analysis of the Crude Reaction Mixture

Retention Time (min)	Compound	% (comp. of total)
1.57	$Me_3SiOSiMe_3$	0.4
2.88	$Me_3SiCH_2CH_2OH$	96.8
4.24	$Me_3SiCH_2CH_2SiMe_3$	0.8
5.37	High molecular wt polymer	2.0

*6', 6%, OV-101 column.

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5. β-TMS ethanol is now available from Aldrich Chemical Company, Milwaukee, Wisconsin.
6. β-TMS ethanol has been prepared by at least three different methods.
   - i. Reaction of ethylbromoacetate and trimethylsilylchloride under Reformatsky conditions followed by $LiAlH_4$ reduction: R.J. Fessenden and J.S. Fessenden, J. Org. Chem., 32, 3535 (1967); see also Ref. 1b. The main drawback is that a low overall yield is obtained after the multistep sequence.
   - ii. Hydroboration of vinyltrimethylsilane: J.A. Soderquist and A. Hassner, J. Organometal. Chem., 156, C12 (1978); J.A. Soderquist and H.C. Brown, J. Org. Chem., 45, 3571 (1980). The authors admit that the reactions are capricious and that both the yield and the ratio of α- and β-(trimethylsilyl)ethanol may vary. The cost of the reagents involved makes the reaction less economically feasible as well.
   - iii. Oxymercuration of vinyltrimethylsilane: J.A. Soderquist and K.L. Thompson, J. Organometal. Chem., 159, 237 (1978). The main complaint with this procedure is that the by-products may interfere with the protection step. Purification by a spinning band distillation is required in order to obtain pure reagent.
7. The reaction can be scaled up or down without difficulty.
8. Available from Petrarch Systems, Levittown, Penna. at very low cost.

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