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THE *cis* REDUCTION OF 4-(TRIMETHYLSILYL)-3-BUTYN-2-OL WITH LITHIUM ALUMINIUM HYDRIDE

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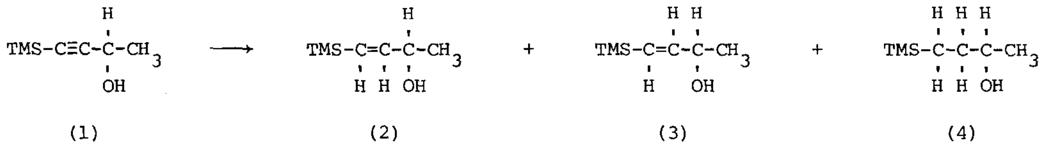
Abstract: *A systematic study led to a method for the preparation of (Z)-4-(trimethylsilyl)-3-buten-2-ol (2) in at least 99% purity by the reduction of the alkyne 4-(trimethylsilyl)-3-butyn-2-ol (1) with lithium aluminium hydride (LAH) as a clear solvate in ether.*

Excellent yields of relatively pure *trans* isomer (3) have been achieved in our laboratory by the reduction of compound (1) by using either LAH in refluxing tetrahydrofuran (THF)[1], or (2-methoxyethoxy)aluminium hydride in ether at room temperature[2]. However, the *cis* isomer (2) with a purity greater than 98% required until now low pressure (1 Atm) catalytic hydrogenation of (1) over P-2 nickel boride poisoned with ethylenediamine[3]. A more convenient method to generate this isomer in quantity was urgently needed. It was felt that reduction with hydrides would be advantageous if the *cis*-stereochemistry could be achieved for this reaction.

Borden *et al.*[4a] were the first to report obtaining a mixture of *cis* and *trans* reduction of a propargylic alcohol using ether as solvent. Later, Djerassi *et al.*[4b] did a study of non-silylated alkynes which showed that as the solvent used in the reduction (with LAH) became less coordinating (weaker Lewis base), the percentage of *cis* isomer could be increased. Since the use of ethyl ether[5] gave a *cis*:*trans* ratio of 40:60 while THF led only to the *trans*-isomer, we felt that the use of ether as solvent might increase the proportion of *cis* isomer.

We initially used lithium dialkoxyaluminium reagents in order to minimize overreduction[6] but subsequently abandoned them because of their low reactivity and in some cases their lack of stereochemical selectivity. The results of our systematic studies are summarized in Table I where it can be seen that the use of ether as solvent tended to increase the proportion of *cis* to *trans*

TABLE I. Reduction of 4-(Trimethylsilyl)-3-Butyn-2-ol



$$\mathrm{TMS{-}C{\equiv}C{-}\overset{H}{\underset{OH}{C}}{-}CH_3} \longrightarrow \mathrm{TMS{-}\underset{H}{C}{=}\underset{H}{C}{-}\overset{H}{\underset{OH}{C}}{-}CH_3} + \mathrm{TMS{-}\underset{H}{C}{=}\overset{H}{C}{-}\overset{H}{\underset{OH}{C}}{-}CH_3} + \mathrm{TMS{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{OH}{C}}{-}CH_3}$$

(1) (2) (3) (4)

Exp.	Reducing Agent	Solvent	Moles of Reducing Agent[a]	Temp.[b] (°C)	Time (h)	Ratio[c] *cis*:*trans*:saturated
1	LAH	THF	0.5	RT → reflux	2.5	4:94:2
2a	$NaAlH_2(OCH_2CH_2OCH_3)_2$	Et_2O	3.2	0 → RT	1.0	0:100:0
b	$NaAlH_2(OCH_2CH_2OCH_3)_2$	Et_2O	3.2	0 → RT reflux	10 min 0.5	0:99:1
3	H_2/NiB	EtOH	1	RT	2	98:2:0
4	LAH	Et_2O	0.5	0 → RT RT RT	1 21 40	70:30:0[d] 55:45:0[e] 55:45:0[f]
5	LAH	Et_2O	0.5	0 → reflux	2.5	70:30:0
6	LAH	Et_2O	0.5	refluxing Et_2O-LAH	2.5	70:30:0
7	LAH	Et_2O	1	0 → reflux	2.5	60:40:0
8	LAH	Et_2O	1	refluxing Et_2O-LAH	2.5	60:40:0
9	LAH	Et_2O	2	RT → reflux	2.5	86:14:0
10	LAH	Et_2O	15	0 → reflux	7.5	55:40:5
11	LAH*(8)	THF	2	RT → reflux	0.5	5:93:2
12	LAH*	Et_2O	2	0 → reflux RT	2.5 8	95:4:1
13	LAH*	Et_2O	2	RT	22	49:8:43
14a	LAH*	Et_2O	2	RT → reflux	0.5	99:1:0
b	LAH*	Et_2O	2	RT → reflux	1.0	98:2:0
c	LAH*	Et_2O	2	RT → reflux RT	1.0 1.0	95:2:3

[a] Per mole of substrate.

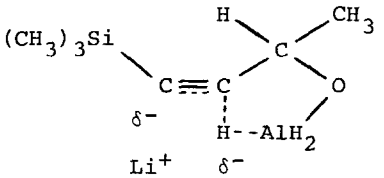
[b] T → reflux signifies addition of the substrate was carried out at the temperature indicated, followed by refluxing for the period of time indicated. Refluxing Et_2O-LAH signifies that the substrate was added to the refluxing suspension.

[c] The relative ratios were obtained from nmr (60 and 200 MHz) and/or from gc. GC conditions: Column: 6% OV101, 2m x 6mm; Temperature: 70° + 4°/min; Retention time (min): *cis*, 2.05; *trans*, 2.33; sat., 2.73.

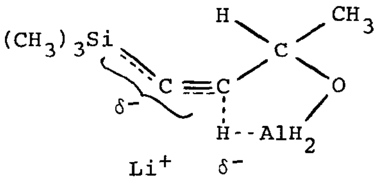
[d] 50%. [e] 75%. [f] 90%. Incomplete reactions estimated by nmr.

isomer in accordance with Djerassi's observation although it should be noted that an excess of *cis*-isomer was consistently obtained. The same trend was also observed by Denmark *et al.*[2] with a similar compound. However, the influence of other parameters such as time, temperature, and nature of the reducing agent on the final outcome remained unpredictable. We finally attempted reduction with a *filtered solution* of LAH in ether. Brown *et al.*[7] recently reported the use of crystal clear solutions[8] of LAH as a reducing medium instead of the usual slurries and noted an unexpected reactivity for such solutions. We felt that since the solution was homogeneous, some surface adsorption effects, when using slurries, would be eliminated and thus allow the reaction to proceed in a more controlled manner. Indeed, this is what we observed. *The use of crystal clear solutions of LAH in ether led to the cis reduction of 4-(trimethylsilyl)-3-butyn-2-ol with a stereoselectivity exceeding 99%.*

No precise explanation offers itself for these observations. If Djerassi's mechanism is extrapolated to our substrate, the transition state involved in the *cis*-reduction may be represented by (A). In the case of non-silylated alkynes in a poor solvating solvent such as ether, the transition state complex (A) may be favored only to the extent of 40%, presumably because of the unfavorable proximity of charges. However, it is known[9] that silicon can stabilize a proximal negative charge which by virtue of it being delocalized as in (A') would increase the probability of transition state (A) for *cis*-reduction.



(A)



(A')

This simple rationalization may not appear adequate although the importance of a poorly solvating solvent (ether) can be appreciated. It is clear that the chemical nature and the physical state of the reducing agent are very important (even critical in this case) in determining the outcome of the reaction. Exactly how time, temperature, surface effects, substrate, *etc.* play a role remains enigmatic at this time[10].

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3. Brown, C.A.; Ahuja, V.K., J. Chem. Soc. Chem. Comm. 1973, 553; and references therein.
4. (a) Borden, W.T., J. Am. Chem. Soc. 1970, 92, 4898.
   (b) Grant, B.; Djerassi, C., J. Org. Chem. 1974, 39, 968.
5. A better choice is isopropyl ether which gave a *cis* to *trans* ratio of 75:25. However, it is not as attractive as ethyl ether as a solvent.
6. Jung, M.E.; Gaede, B., Tetrahedron 1979, 35, 621; see note 5 of Ref. 2.
7. Krishnamurthy, S.; Brown, H.C., J. Org. Chem. 1982, 47, 276.
8. Clear solutions of LAH (LAH*) were prepared as described in Ref. 7 except that the suspension was stirred for 20 h at r.t. in dry solvent prior to filtering through celite under dry nitrogen. These solutions were stable for at least several weeks when kept under nitrogen in a septum sealed flask at r.t. although some evaporation of solvent did occur. Molarity of the solutions was determined by titration.
9. Zweifel, G.; Murray, R.E.; On, H.P., J. Org. Chem. 1981, 46, 1292; and references therein.
10. When 3-butyn-2-ol was reduced in ether with LAH*, a ratio of about 30:70 *cis* to *trans* was obtained. This result is practically the same as that reported by Djerassi *et al.* (obtained with the use of LAH as a slurry in ether) and would suggest that the effect exerted by the silyl group is a necessary condition for *cis* reduction. While the effect of the silyl group may be essential, it is clear that it is not sufficient by itself to control stereoselective reduction.

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