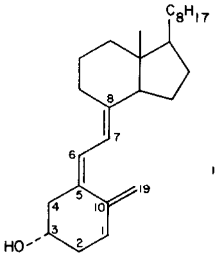
Tetrahedron Letters No. 39, pp 3635 - 3636.
0040-4039/78/0922-3635$02.00/0

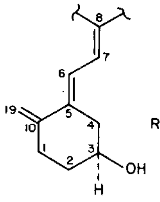
HYDROZIRCONATION-PROTONATION OF VITAMIN D[1]

Alan W. Messing, Frederick P. Ross, Anthony W. Norman and William H. Okamura*
Departments of Chemistry and Biochemistry
University of California, Riverside, California 92521 USA

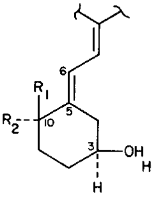
In an effort to improve on prior art utilizing 9-borabicyclo[3.3.1]nonane (9-BBN) for effecting regiospecific reduction of the $\Delta^{10(19)}$ double bond and subsequent 19-functionalization (with H or X) of vitamin D_3 (**1**) and its 5E-isomer (**2**),[2] we have investigated the reaction of **1** and **2** with Schwartz's reagent $[(\eta^5\text{-}C_5H_5)_2Zr(Cl)H$ abbreviated Zr-H].[3] Hydrozirconation with this reagent would appear to be operationally simpler and faster than the analogous hydroboration procedures. Moreover, protonation of 9-alkyl-9-BBN adducts (e.g., those derived from **1** and **2**) is generally a poor reaction, while protonation of alkylzirconium compounds is reportedly an excellent reaction. We were also cognizant of the fact that the action of Zr-H on complex conjugated trienes had not been previously reported.



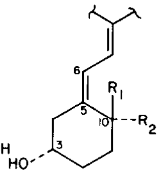
1 (5Z)



2 (5E)



3 (5E)



4 (5Z)

a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

In a typical procedure, solid steroid (100 mg) and Zr-H (see Table) were admixed and placed under argon in a septum capped vessel containing a magnetic stirring bar. Benzene (4 mL, freshly distilled from potassium-benzophenone ketyl under argon) was introduced by syringe and the flask was warmed to 40°C. At the requisite time, the reaction was quenched by addition of $\sim$0.1M hydrochloric acid (10 mL). Conventional work up was followed by chromatographic separation of products.[4] The results for a series of experiments are recorded in the Table. As can be seen from entry 3, the reaction of **2** is complete after only one hour using stoichiometric proportions of Zr-H and **2** (2:1). The sterically more congested 5Z-isomer **1** reacts significantly more slowly (compare entries 2 and 3). It is indeed clear that hydrozirconation-protonation is superior to 9-BBN hydroboration-protonation for preparing **3** and **4**. The new procedure is operationally simpler, faster and provided higher yields of products. Neither the old[2a] nor new procedure afforded any significant stereoselectivity however.

A very interesting result is that 5Z⇄5E isomerization occurred during hydrozirconation-protonation. It is significant that the four dihydrovitamins **3a**, **3b**, **4a** and **4b** are recovered unchanged upon being subjected to conditions more severe (2 molar equivalents of Zr-H for 5-6 hrs at 40°) than the conditions used for their preparation. Moreover, there is no evidence of any **2** in reactions of **1** and vice versa. In an attempt to reverse the reaction between Zr-H and **1**, excess 1-hexene (30 molar-equivalents) was added to the reaction (**1** + three molar equivalents of Zr-H as above) after 1 hr. No effect was seen on product distribution and no **1** or **2** was detectable.[5]

TABLE[a]

Steroid (mmol)	Zr-H (mmol)	Benzene (mL)	t(hrs)	yields (based on steroid) **3a** 5E,10R	 **3b** 5E,10S	 **4a** 5Z,10S	 **4b** 5Z,10R
5Z-D_3(0.26)[b]	(0.82)	4.0	1.0	15%	trace[c]	32%[c]	37%
5Z-D_3(0.26)	(0.54)	4.0	21	($\gtrsim$75% unreacted 5Z-D_3)			
5E-D_3(0.28)[d]	(0.59)	4.0	1.0	35%	36%	trace	6.5%
5E-D_3(0.36)	(1.15)	5.5	<0.17	(unreacted 5E-D_3 not detectable by TLC)			
5E,10R(0.054)	(0.12)	0.9	5.0	95%	---	---	---
5E,10S(0.056)	(0.13)	0.9	5.0	---	74%	---	---
5Z,10S(0.056)	(0.13)	0.9	5.0	---	---	~100%	---
5Z,10R(0.090)	(0.19)	1.4	6.0	---	---	---	77%

[a] At 40° under an inert atmosphere with magnetic stirring, absolute weighed yields are given; [b] In a separate experiment, 1-hexene (8.0 mmol) was added and then the mixture stirred for 2 additional hours. No change (NMR, TLC) was observed; [c] The less efficient dry column chromatography method (see footnote 4) was used. The two 10S-isomers were inseparable. The ^{1}H-NMR is identical to that of TLC pure 5Z-10S isomer, but TLC reveals the presence of a trace amount of 5E,10S isomer; [d] Products were separated by the efficient wet column (see footnote 4) method.

Acknowledgments. We are grateful to Professor Michael F. Rettig for helpful discussions and to the National Institutes of Health (USPHS Grants AM-16595 and AM-09012) for generous support of this work. F.P.R. acknowledges the South African Council for Scientific and Industrial Research for a Scholarship. The crystalline vitamin D_3 was a generous gift from Dr. M. Rappoldt of Philips-Duphar (Weesp, the Netherlands).

References and Notes

1. Paper 17 in the series, Studies on Vitamin D (Calciferol) and Its Analogs. For paper 16, see M. L. Hammond, A. Mouriño and W. H. Okamura, J. Am. Chem. Soc., in press.
2. (a) W. H. Okamura, M. L. Hammond, A. Rego, A. W. Norman and R. M. Wing, J. Org. Chem., **42** 2284 (1977); (b) A. Mouriño and W. H. Okamura, ibid., **43**, 1653 (1978).
3. J. Schwartz and J. A. Labinger, Angew. Chem. Int. Ed. Engl., **15**, 333 (1976) and references cited. The Zr-H used in this study was commercial material (Alfa-Ventron Corp.). Schwartz's reagent was first studied by Wailes and co-workers: B. Kautzner, P. C. Wailes and H. Weigold, Chem. Commun., 1105 (1969) and P. C. Wailes, H. Weigold and A. P. Bell, J. Organometal. Chem., **43**, C32 (1972).
4. TLC and NMR analyses were conducted at each stage of purification. Chromatography was carried out on dry silica gel (80 x 1 cm; 1:1 mixture of ether and 30-60° low boiling petroleum ether, lbpe) or preferably on a similar wet silica gel column [% ether in lbpe (mL): 5% (50), 7.5% (100), 10% (100); 20% (200), 50% (250). After discarding the first 175 mL of eluant, the following fractions were collected: #1-45 (1.8 mL), #46-90 (2.7 mL), #90-130 (4.5 mL)]. The latter method will separate all four isomers **3** and **4** in a single pass.
5. A similar experiment using ethylene to recover olefin from an alkyl zirconium also failed (cited in the review article by Schwartz and Labinger, reference 3).

(Received in USA 12 June 1978; received in UK for publication 24 July 1978)