Tetrahedron Letters,Vol.25,No.42,pp 4749-4752,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

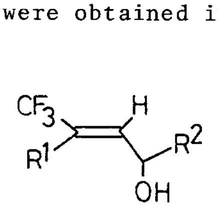
HYDROMETALLATION OF 1-ALKYL-3-TRIFLUOROMETHYL PROPARGYL ALCOHOLS

Yuji Hanzawa, Kei-ichi Kawagoe, Naomi Tanahashi and Yoshiro Kobayashi*

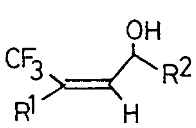
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, JAPAN

Summary: The hydrometallation of trifluoromethylated propargyl alcohol derivatives with metal hydride reagents proceeds smoothly to give cis- and trans-olefins on H_2O quenching. The halodemetallation of intermediate formed in the reaction process was also examined.

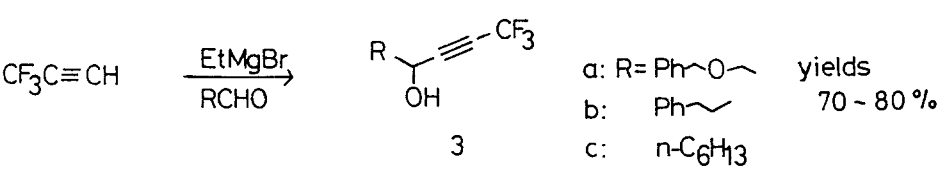
For the study of the synthesis of biologically active fluorine-containing molecules, it was necessary to synthesize trifluoromethylated allylic alcohols (1,2) in a regio- and stereoselective manner as a synthetic fragment. These molecules are considered very important to construct polyolefin compound which shows an interesting biological activity.[1)] Although a few methods are available for the preparation of these compounds (1,2),[2)] it is still needed to explore other possibilities. Recent advances in acetylenic compound chemistry[3)] prompted us to carry out the hydrometallation of trifluoromethylated acetylenic compounds. For this purpose, we used propargyl alcohol derivatives (3), because of their ease in handling and preparation and more importantly, the existence of chiral center in 3 which may possibly facilitate the synthesis of trifluoromethylated chiral compounds.[4)] The starting materials were obtained in the conventional manner.[5)]



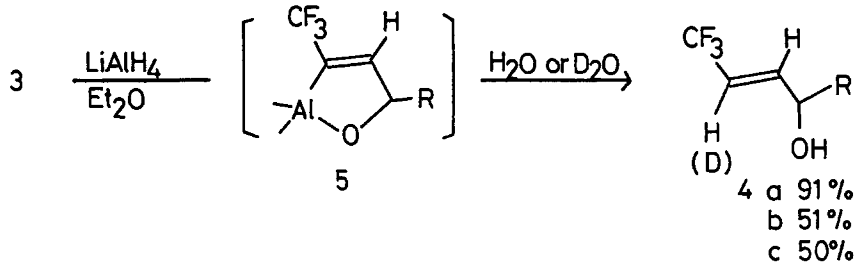
1

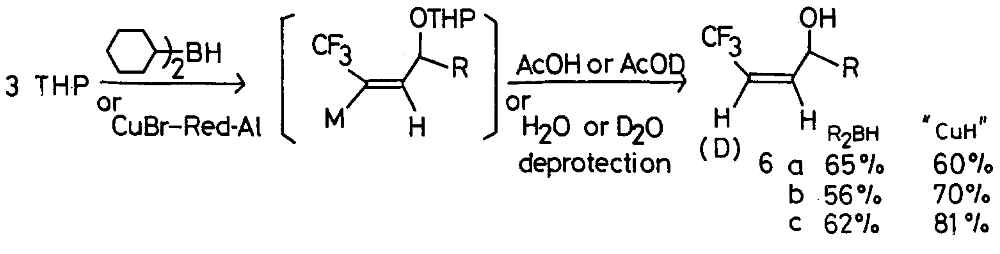


2

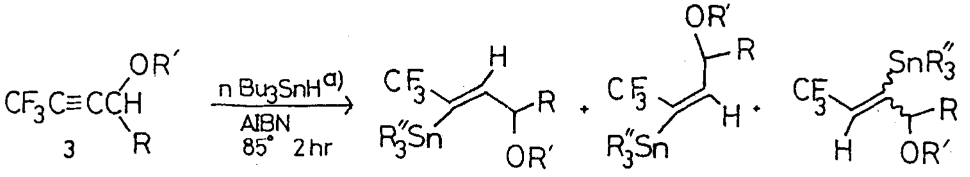


The reduction of propargyl alcohol system with lithium aluminum hydride (LAH) had been examined by many workers[6] and it is known that the basicity of the solvent used and the structure of propargyl alcohol affect the stereo- and regioselectivities of the hydrometallation. In the case of 3, trans allylic alcohols(4) were obtained[7] (LAH, Et$_2$O, -78°, 30min.) in 50-90% yields. Quenching of the reaction mixture with deuterium oxide gave a deuterated compound whose NMR spectrum showed that deuteration occurred only at the carbon bearing a trifluoromethyl group in all cases.[8] This means that cyclic ate-complex(5) is present as an intermediate as postulated before.[9] The cis reduction[10] was achieved by hydroboration-protonation[11] or copper hydride reduction.[12] Hydroboration of protected alcohols (3, THP) with dicyclohexylborane at -20~0°, followed by protonation and deprotection with acetic acid gave cis allylic alcohols (6) in 56-65% yields. In the case of the copper hydride (generated from CuBr and Red-Al at -5° in THF) reduction of protected alcohols (3, THP) at -78°, followed by gradual warming up to room temperature, compounds 6 were obtained in 60-81% yields. The regiochemistry of these hydrometallations was also proven by deuterium trapping experiments (CH_3COOD and D_2O respectively). In both cases, deuteriums were incorporated only at CF_3SP^2 carbon.[8] These experiments show the very strong directive effect of the trifluoromethyl group in hydrometallation.





The hydrostannation of propargyl alcohols has been studied[13] for the preparation of functionalized vinylhalide. The results of the hydrostannation of 3a and 3a-THP are summarized in Table I. These products could easily be separated by flash column chromatography and characterized by NMR spectrum. The structure of the main product was determined by the tin-hydrogen coupling constant ($J_{Sn^{117}-H}$= 83Hz).[14]



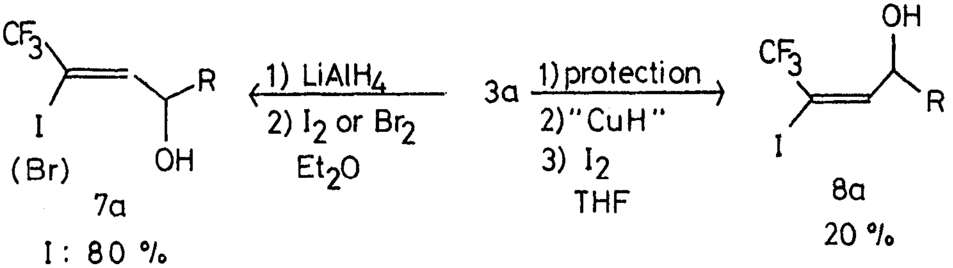
R = Ph⌒O⌒ R' = THP	ratio	15	1	1	Y. 87 %
	n Bu₃SnH a) 85° 2hr → ratio	30	1	6	Y. 63 %
R = Ph⌒O⌒ R' = H	n Bu₃SnH a) AIBN 85° 2hr → ratio b)	11	3	1	Y. 62 %

a) 2.3eq. of n-Bu_3SnH relative to 3 was used and the mixture was heated at 85° for 2hr under an Ar atmosphere.

b) The trans-reduced product 4a was also obtained in a 16% yield.

Table I

On the basis of the hydrometallations, we examined the halodemetallation of the intermediates formed in the reaction process. When the ate-complex (5a) was treated with a large excess of iodine (or bromine) at -78°, vinyliodide (or bromide)(7a) was obtained in a 80% yield (85% yield for bromide).[15] The vinyliodide (8a)—stereoisomer of 7a—was obtained in a 20% yield[7] by iodine quenching of the copper hydride reduction reaction. The hydrostannated products resisted iodination (I_2, CH_2Cl_2, r.t.) but, under more polar conditions,[16] this was achieved in 5~10% yields (I_2, MeOH, 30°). The hydroborated intermediates gave no substituted products on treatment with electrophiles even under the ate-complex forming conditions,[17] only a complex reaction mixture containing no fluorine atoms being formed. Using these compounds (7a, 8a), an attempt is now being made to synthesize a biologically active fluorine-containing compound.



7a

I : 80 %

Br: 85 %

8a

20 %

References and Notes

1) W. Gärtner, D. Oesterhelt, P. Towner, H. Hopt and L. Ernst, J. Am. Chem. Soc., 103, 7642 (1981). A. E. Asato, D. Mead, M. Denny, T. T. Bopp and R. S. H. Liu, J. Am. Chem. Soc., 104, 4979 (1982).
2) F. Camps, R. Canela, J. Coll, A. Msseguer and A. Roca, Tetrahedron, 34, 2179 (1978). C. D. Poulter, P. L. Wiggins and T. L. Plummer, J. Org. Chem., 46, 1532 (1981). T. Kitazume and N. Ishikawa, Chem. Lett., 1453 (1982).
3) J. F. Normant, Synthesis, 841 (1981) and the references cited therein.
4) It is known that optically active propargyl alcohol derivatives can be obtained by asymmetric syntheses or by resolution.
5) J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Saret and S. L. Steelman, J. Am. Chem. Soc., 83, 4663 (1961). F. G. Drakesmith, O. J. Stewart and P. Tarrant, J. Org. Chem., 33, 280 (1968).
6) a) B. Franzus and E. I. Snider, J. Am. Chem. Soc., 87, 3423 (1965). b) E. I. Snider, J. Org. Chem., 32, 3531 (1967). c) idem, J. Am. Chem. Soc., 91, 2579 (1969). d) E. J. Corey, J. A. Katzenellenbogen and G. H. Posner, J. Am. Chem. Soc., 89, 4245 (1967). e) W. T. Borden, J. Am. Chem. Soc., 92, 4898 (1970). f) B. Grant and C. Djerassi, J. Org. Chem., 39, 968 (1974).
7) All new compounds were identified by their NMR, IR and mass spectra.
8) A Varian EM-390 spectrometer was used. Accuracy of the NMR analysis of deuterated sample is considered to be more than 90%.
9) ref. 6) e).
10) Catalytic partial hydrogenation (Pd-$BaSO_4$, quinoline, MeOH) also gave cis allylic alcohol (70%).
11) J. Plamondon, J. T. Snow and G. Zweifel, Organomet. Chem. Syn., 1, 249 (1971).
12) M. F. Semmelhack, R. D. Stauffer and A. Yamashita, J. Org. Chem., 42, 3180 (1977).
13) M. E. Jung and L. A. Light, Tetrahedron Lett., 23, 3851 (1982). H. E. Ensley, R. R. Beuscher and K. Lee, J. Org. Chem., 47, 404 (1982).
14) W. R. Cullen and G. E. Styan, J. Organometal. Chem., 6, 117 (1966). A. J. Leusink, H. A. Budding and J. W. Marsman, J. Organometal. Chem., 9, 285 (1967).
15) ref. 6) d). G. Stork, M. E. Jung, E. Colvin and Y. Noel, J. Am. Chem. Soc., 96, 3684 (1974).
16) P. Baekelmams, M. Gielen, P. Malfroid and J. Nasielski, Bull. Soc. Chim. Belg., 77, 85 (1968).
17) K. Uchida, K. Utimoto and H. Nozaki, J. Org. Chem., 41, 2941 (1976).

(Received in Japan 14 June 1984)