Tetrahedron Letters,Vol.23,No.44,pp 4607-4610,1982 0040-4039/82/444607-04$03.00/0
Printed in Great Britain

A NEW METHOD FOR THE CONVERSION OF ALDEHYDES (RCH_2CHO) TO ACETYLENES ($RC{\equiv}CH$) *VIA* 1-ALKENYLSTANNANES. APPLICATION TO THE SYNTHESIS OF 9(O)-THIA-Δ^6-PGI_1

Masakatsu Shibasaki, Yasuhiro Torisawa, and Shiro Ikegami*
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

Summary: A method for the conversion of aldehydes to acetylenes via 1-alkenylstannanes is reported, including its application to the synthesis of 9(O)-thia-Δ^6-PGI_1.

In connection with studies directed toward the synthesis of prostacyclin analogs, it was required to develop a mild method for the transformation of aldehydes (RCH_2CHO) to acetylenes ($RC{\equiv}CH$),[1] hopefully *via* 1-alkenylstannanes. In this communication, we wish to report a solution to this problem as well as its successful application to the synthesis of 9(O)-thia-Δ^6-PGI_1 (26).

Previously we have reported a general method for the preparation of α-haloalkylstannanes from aldehydes.[2] Therefore, if the dehydrohalogenation of α-haloalkylstannanes occurs readily to lead to 1-alkenylstannanes, it occurred to us that a series of reactions ($RCH_2CHO \longrightarrow RCH_2CH(X)Sn(n\text{-}Bu)_3 \longrightarrow RCH{=}CHSn(n\text{-}Bu)_3 \longrightarrow RC{\equiv}CH$) would offer a solution to this problem.[3] In the first place, our assumption was tested using the simple model compound (1). The aldehyde (1) was converted to the quite stable α-bromoalkylstannane (2)[4] by the method reported by us[2] in 80% overall yield from 1. Treatment of 2 with 3 equiv of DBU in toluene at 110°C for 2 hr was found to afford the vinylstannane derivative (3) in excellent yield. The vinylstannane derivative (3) was further treated with lead tetraacetate in acetonitrile according to Corey's method,[3] providing the terminal acetylene (4)[4] in 65% overall yield from 2. Thus, a new mild method for the conversion of aldehydes to acetylenes *via* 1-alkenylstannanes was realized. The method described above could be applied to more complex molecules including functionalities such as a double bond, an epoxide, a *t*-butyldimethylsilyl ether and a THP ether. The results are summarized in Table I.

Stereochemistry of the vinylstannane derivative (3) was determined by the PMR spectrum and further the GLC analysis,[5] showing that the *E*-isomer was formed as the major product in a ratio of *ca.* 8(*E*):1(*Z*).[6] Interestingly, this stereoselectivity was slightly superior to that of hydrostannation of 5-phenyl-1-pentyne (*E*:*Z*= *ca.* 7:1).

It is generally known that the Shapiro reaction, which provides alkenyllithiums from carbonyl compounds *via* tosylhydrozones, is limited to the case of ketones.[7] Therefore, the present reaction opens the new method for the preparation of 1-alkenylithiums from corresponding aldehydes, since alkenylstannanes are readily convertible to alkenyllithiums.[8]

By the use of this methodology, aldehydes can be converted to a variety of useful compounds as summarized in Scheme I.

In the case of aldehydes possessing a substituent on the α-carbon atom, α-bromoalkylstannanes are generally obtained as a mixture of diastereomers. Accordingly, it was anticipated that separation of stereoisomers, followed by dehydrobromination, would produce stereochemically

Scheme I

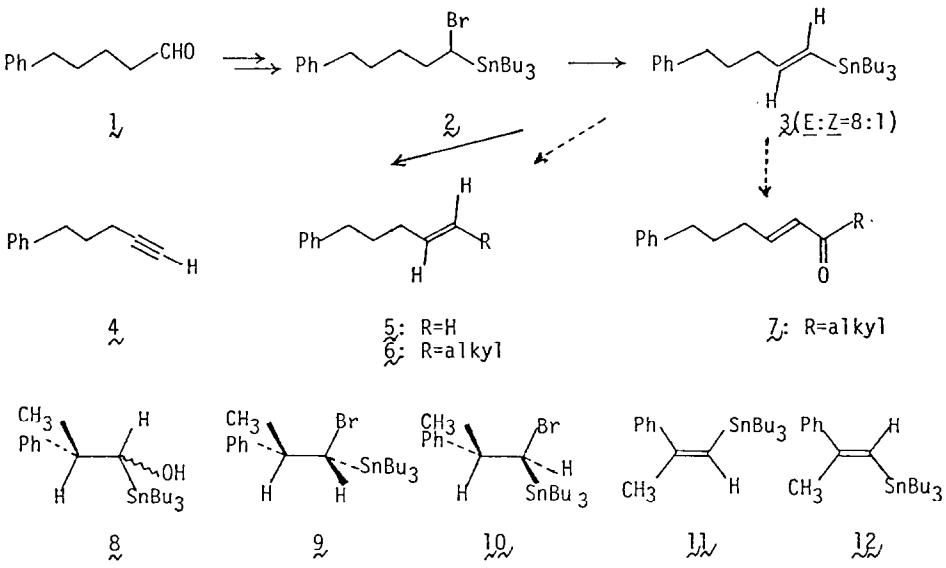


Table I. Conversion of Aldehydes to Acetylenes *via* α-Bromoalkylstannanes

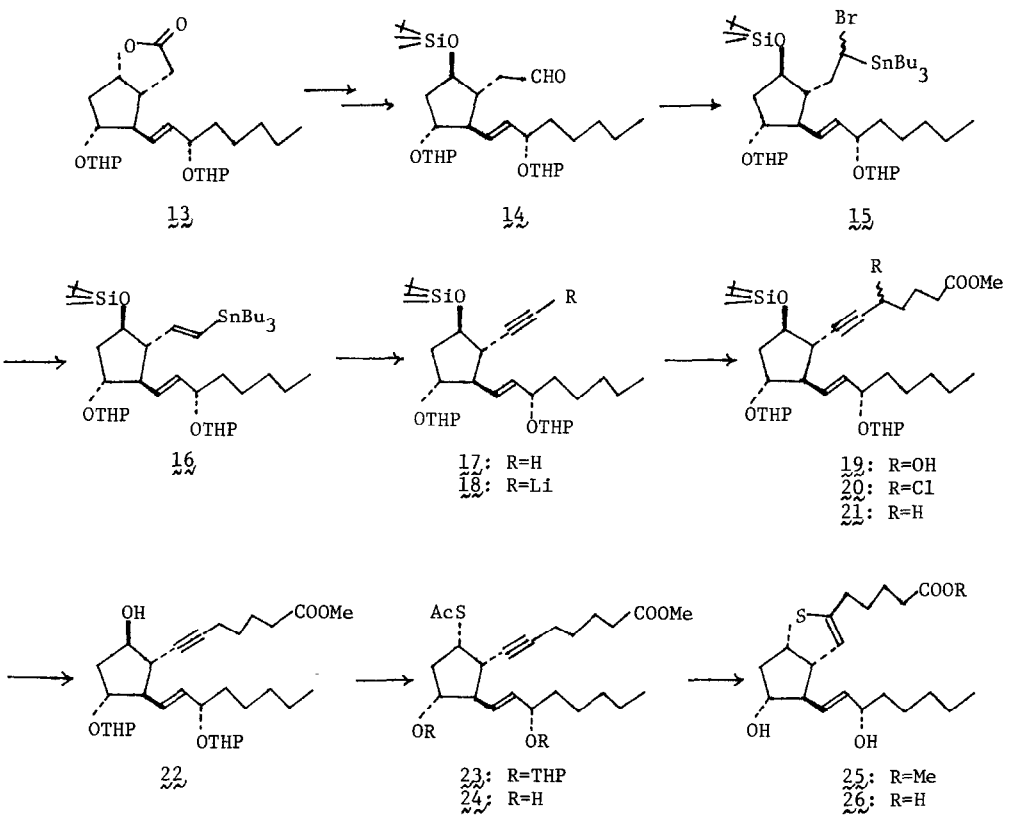
RCH_2CHO (I) ⟶ $RCH_2CH(Br)Sn(n\text{-}Bu)_3$ (II) ⟶ $RC{\equiv}CH$ (III)

Entry	R	II % Yield from I	III % Yield from II
1	$Ph(CH_2)_2CH{=}CH(CH_2)_2-$	70	55
2	$Ph(CH_2)_2CH(O)CH(CH_2)_2-$	67[a,b]	55
3		65[a]	54
4		65[a]	64

a, Yields were calculated on the basis of the recovery of starting aldehydes (*ca.*5%). b, Since there was obtained a small amount of the bromohydrin, probably formed through epoxide opening by HBr, the crude reaction mixture was treated with DBU in toluene at room temperature.

pure 1-alkenylstannanes. This was found to be the case. Using Still's method, 2-phenylpropionaldehyde was converted to the α-hydroxyalkylstannane (8), which was subsequently treated with Ph_3P-diethyl azodicarboxylate (DAD)-CH_2Br_2 in benzene at reflux temperature, affording the α-bromoalkylstannanes (9 and 10) in a ratio of 9:1 (40% overall yield from the aldehyde).[9] The major stereoisomer (9),[4] which was separated from 10[4] by preparative TLC technique, was transformed to the stereochemically pure *Z*-vinylstannane derivative (11) in excellent yield: PMR ($CDCl_3$) δ5.85 (1H, broad s), while the *E*-isomer (12): PMR($CDCl_3$) δ6.20 (1H, s), was exclusively obtained from the other stereoisomer (10).

Generality of the present method was further demonstrated by applying to the synthesis of 9(O)-thia-Δ^6-PGI_1 (26). The starting aldehyde (14),[4] which was prepared from the well-known lactone (13) in six steps (57% overall yield),[10] was converted to the α-bromoalkylstannane (15)[4] (two steps,[2] 54% yield). The terminal acetylene (17)[4] was then obtained *via* the vinylstannane derivative (16)[11] in 63% yield by the method described above. The coupling of the lithium acetylide (18) with methyl 4-formylbutylate afforded the propargylic alcohol (19)[4] in nearly quantitative yield. Crucial deoxygenation of 19 was accomplished by converting it to the propargylic chloride (20) (5 equiv of CCl_4, 3.3 equiv of HMP, ether) followed by treatment with tri-*n*-butyltin hydride in toluene. Under these conditions, none of the allenes was observed in the reaction mixture. Cleavage of the *t*-butyldimethylsilyl group in 21 afforded the 9β-alcohol (22)[4] in 60% overall yield from 19. The 9β-alcohol (22) was then efficiently converted to the 9α-thioacetate (23)[4] by the method of Volante (70% yield).[12] Cleavage of the THP groups in 23 led cleanly to 24[4] (83% yield), which was followed by treatment with excess potassium carbonate in methanol to provide the *endo*-enol thioether (25)[4] in 66% yield. Comparison of its spectral data with those of an authentic sample[13] confirmed their identity. Finally 25 was hydrolyzed by treatment with lithium hydroxide in THF-H_2O (3:1), followed by acidification with pH 4.01 buffer solution, leading to 9(O)-thia-Δ^6-PGI_1 (26) in 78% yield.



Acknowledgment. The financial support to this research by Suzuken, Kenzo Memorial Foundation and by Grand-in-Aid for Scientific Research extended from the Ministry of Education, Science and Culture is gratefully acknowledged.

References and Notes

(1) For the synthesis of acetylenes from carbonyl compounds using the harsh conditions, see (a) T.L.Jacobs, Organic Reactions, 5, 1 (1949); (b) E.V.Dehmlow and M.Lissel, Justus Liebigs Ann. Chem., 1 (1980) *and other references cited therein.*

(2) Y.Torisawa, M.Shibasaki, and S.Ikegami, Tetrahedron Lett., 22, 2397 (1981).

(3) Transformation of 1-alkenylstannanes to terminal acetylenes has been established, see E.J.Corey and R.H.Wollenberg, J. Am. Chem. Soc., 96, 5581 (1974).

(4) Satisfactory spectroscopic data (mass, PMR, IR spectra) were obtained for this substance.

(5) For the determination of stereochemistry of 1-alkenylstannanes, see (a) E.J.Corey, P.Ulrich, and J.M.Fitzpatrick, J. Am. Chem. Soc., 98, 222 (1976); (b) D.Seyferth and L.G.Vaughan, J. Organometal. Chem., 1. 138 (1963).

(6) Addition of tri-*n*-butyltin hydride and a small amount of AIBN, followed by heating, did not produce any change on the product ratio, see S.-M.L.Chen, R.E.Schaub, and C.V. Grudzinskas, J. Org. Chem., 43, 3450 (1978).

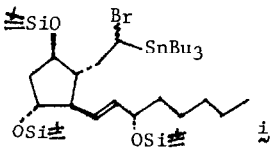
(7) E.Vedejs and W.T.Stolle, Tetrahedron Lett., 135 (1977).

(8) See for example S.-M.L.Chen, R.E.Schaub, and C.V. Grudzinskas, J. Org. Chem. 43, 3450 (1978).

(9) This product ratio was nearly corresponding to that of the alcohol (8) (*ca.* 9:1). The use of the halogenation conditions (CBr_4-Ph_3P in CH_2Cl_2) led to 11 and 12 in a ratio of 2:1, probably due to the interference of HBr generated in the reaction medium.

(10) (i) LiOH, H_2O-DME, then oxalic acid, (ii) CH_2N_2, (iii) DAD-Ph_3P-PhCOOH, THF, (iv) K_2CO_3, MeOH, (v) *t*-butyldimethysilyl chloride-imidazole, DMF, (vi) DIBAH, toluene.

(11) Determination of stereochemistry of the newly formed double bond was fairly difficult owing to the presence of THP ethers. Therefore, it was tentatively assigned (*E*:*Z*=10:1) on the basis of stereochemistry of the vinylstannane derivative (ii) prepared from i. It is also noted that this methodology would solve the problem to introduce a *trans* double bond at the 6-7 position of PGs in a stereocontrolled manner.



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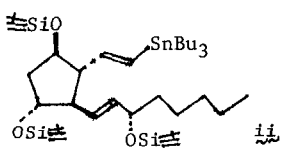

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(12) R.P.Volante, Tetrahedron Lett., 22 3119 (1981).

(13) (a) M.Shibasaki, Y.Torisawa, and S.Ikegami, Chemistry Lett., 1247 (1980); (b) H.Yokomori, Y.Torisawa, M.Shibasaki, *and* S.Ikegami, Heterocycles, 18, 251 (1982).

(Received in Japan 29 July 1982)