Pergamon

Tetrahedron Letters, Vol. 35, No. 6, pp. 823-824, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0370-Y

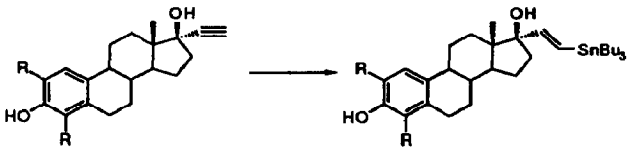
Preparation of Steroidal Vinylstannanes by Stannylcupration of Ethynylestradiols

Clark H. Cummins

Dow Chemical Co., Bldg. 1707, Midland, MI 48674, USA

Abstract: Hydrostannylation of 2,4-dibromo-17α-ethynylestradiol results in both vinylstannane formation and reductive dehalogenation of the A-ring bromides. An alternative approach based upon alkyne stannylcupration was developed, and compared with hydrostannylation on a series of four A-ring substituted ethynylestradiols.

Radioiododestannylation has become an important technique for the preparation of radiolabeled steroids.[1] Consequently, the vinylstannane substrates employed in this process, particularly 17α-stannylvinylestradiols, are quite often the primary synthetic targets for radiopharmaceutical preparation. The *cis*-addition of tributyltin hydride across the triple bond of an alkynyl steroid (Scheme 1) is well known, and constitutes the standard method for the preparation of steroidal vinylstannanes. For example, hydrostannylation of ethynylestradiol (**1a**) has been reported,[2] providing 17α-stannylvinylestradiol (**2a**) in 70-90% yields (in our hands this transformation proceeded in 87%). As part of a program aimed at studying A-ring substituted estradiols, we attempted to employ this strategy in the preparation of 2,4-dibromo-17α-[^{125}I]iodovinylestradiol. Not surprisingly, we encountered difficulties in the hydrostannylation step , as a result of the reducing ability of tributyltin hydride with respect to aryl bromides. When 2,4-dibromo-17α-ethynylestradiol (**1b**) was treated with tributyltin hydride and AIBN in refluxing THF, **2a** was isolated as the major product. Variation of these conditions was ineffective in eliminating reduction of the arylbromides. An examination of alternative methods for the preparation of vinylstannanes suggested the possibility of stannylcupration of the acetylenic steroid.[3] We were quite pleased to find that the reaction of a higher-order stannyl cuprate with acetylene **1b** afforded *trans*-vinylstannane **2b** in 44% yield.



1a	R = H	**2a**	R = H	78%	(87%)
b	R = Br	**b**	R = Br	44%	(0%)
c	R = Cl	**c**	R = Cl	71%	(10%)
d	R = Me	**d**	R = Me	51%	(20%)

Scheme 1. Preparation of steroidal vinylstannanes from the corresponding alkynes via stannylcupration (hydrostannylation yields are in parentheses).

We have studied both the hydrostannylation (Bu_3SnH)[4] and stannylcupration ($Bu_3Sn(Bu)CuCNLi_2$)[5] of four steroidal alkynes (Scheme I). Our results indicate that in some instances stannylcupration is the preferred route to *trans*-17α-stannylvinyl steroids. In fact, for all but the unsubstituted estradiol **1a**, the stannylcupration yields are superior. For steroids **1b** and **1c**, the improved yields could most likely be attributed to the difference in reactivity of the A-ring halides with a stannylcuprate relative to a tin hydride reagent, while the rationale for the case of **1d** is not clear.

Because of the stereochemistry of the stannylcupration process, this method is limited to the preparation of *trans*-vinylstannanes. In addition, the propensity of stannylcuprates to undergo conjugate addition to enones probably makes this method unsuitable for use in the preparation of radiolabeled progesterone receptor ligands. Nevertheless, especially in those cases where the reducing ability of tributyltin hydride presents a problem, stannylcupration of ethynyl steroids offers an attractive alternative to hydrostannylation.

REFERENCES AND NOTES

1. Hanson, R. N. In *New Trends in Radiopharmaceutical Synthesis, Quality Assurance, and Regulatory Control*; A. M. Emran, Ed.; Plenum Press: New York, 1991; pp 303-315.
2. Ali, H.; Rousseau, J.; Ghaffari, M. A.; van Lier, J. E. *J. Med. Chem.* **1988**, *31*, 1946-1950.
3. Barbero, A.; Cuadrado, P.; Fleming, I.; González, A. M.; Pulido, F. J. *J. Chem. Soc., Chem. Comm.* **1992**, 351-353.
4. Typical procedure: A solution of 1.00 g (3.37 mmol) of ethynyl estradiol, 3.63 mL (3.93 g, 13.5 mmol) of tributyltin hydride, and 0.12 g (0.70 mmol) of azobis(isobutyrylnitrile) in 25 mL of tetrahydrofuran was heated at 70°C for 1 h. Evaporation of the solvent at reduced pressure on a rotary evaporator afforded a colorless semi-solid, which was purified by flash chromatography on silica gel, using 20% ethyl acetate in hexane as eluant to afford 1.728 g (87%) of *trans*-vinylstannane **2a**.
5. Typical procedure: A solution of 1.28 mL (1.47 g, 2.53 mmol) of bis(tributyltin) in 5 mL of tetrahydrofuran was stirred under nitrogen at -20°C as 1.58 mL (2.53 mmol) of a 1.6 *M* solution of n-butyllithium in hexanes was added dropwise. The solution was stirred for 15 min, and then was treated wtih an additional 1.58 mL (2.53 mmol) of a 1.6 *M* solution of n-butyllithium in hexanes. Solid copper (I) cyanide (0.23 g, 2.53 mmol) was then added, and stirring was continued for 15 min. The reaction was cooled to -78°C, and a solution of 0.25 g (0.84 mmol) of ethynylestradiol in 2 mL of tetrahydrofuran was added. The cooling bath was removed, stirring was continued for 2.5 h. The solution was treated with 2 mL of methanol, was stirred for 10 min, and was then treated with 20 mL of 9:1 saturated aqueous ammonium chloride:concentrated aqueous ammonium hydroxide. The mixture was extracted with two 25-mL portions of ethyl acetate, and the organic extracts were combined and dried (Na_2SO_4). Filtration and evaporation at reduced pressure afforded a pale yellow oil, which was purified by flash chromatography on silica gel using 25% ethyl acetate in hexane as eluant to provide 0.384 g (78%) of vinylstannane **2a**.

(*Received in USA* 18 *October* 1993; *revised* 18 *November* 1993; *accepted* 19 *November* 1993)