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Unexpected Reversal in Stereochemistry of Radical Alkyne Cyclisation

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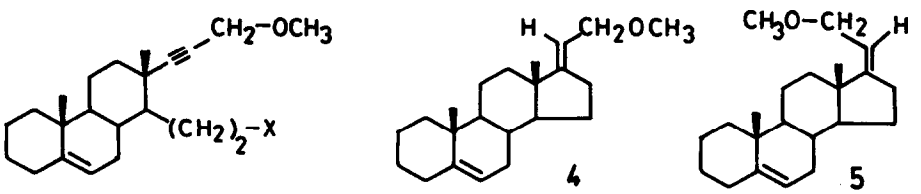
Abstract : Reductive cyclisation with Bu_3SnH (0.07 M) of the secosteroidal alkyne iodide **2** and alkyne dithiocarbonate **3** gave stereoselectively **E**-21-methoxy-pregna-5, 17(20)-diene, **4.** With Bu_3SnH (2.4 M) **2** again gave only **4** whereas **3** gave a 7:3 ratio of the **Z:E** isomers **5:4.** An explanation is put forward invoking a Barton intermediate.

As a part of our investigation of the stereochemistry of radical alkyne cyclisations using secosteroidal substrates[2] we converted the alcohol **1** to the iodide **2** and the dithiocarbonate (xanthate) **3**[3] to be used as substrates for the study of reductive cyclisation with Bu_3SnH. **Scheme 1** gives the structures of the three products expected namely **4, 5** and **6.**



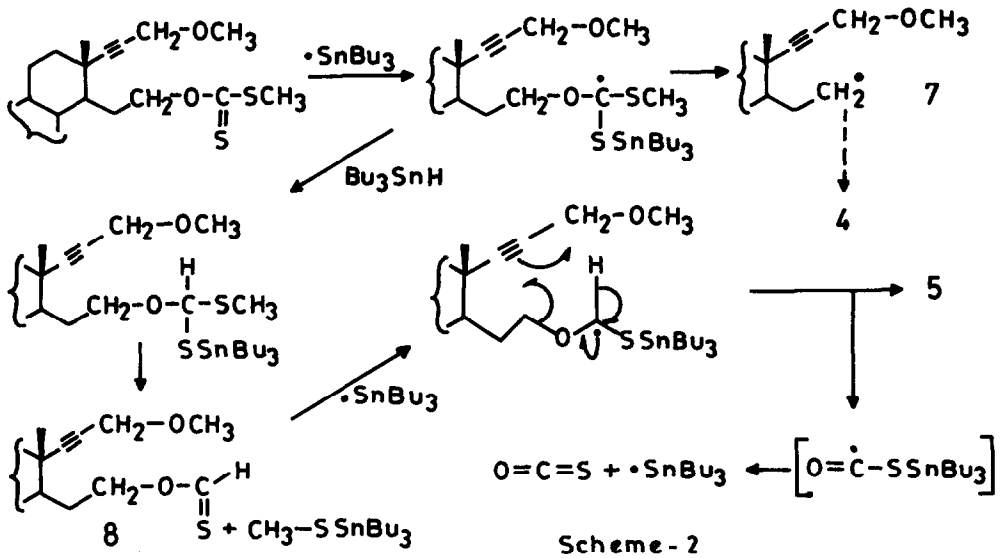
1. X = OH , 2. X = I

3. X = O–C(=S)–SCH3 , 6. X = H

Scheme 1

These should arise from reaction of the intermediate primary radical **7** expected to be produced by the action of Bu_3SnH on both the iodide **2** and the xanthate **3.** Mechanism of formation of **7** from xanthate is given in **Scheme 2**[4]. Irrespective of its mode of formation, radical **7** is expected to attack the **unactivated** alkyne irreversibly[5] to generate a mixture of fast interconverting vinyl radicals[6]. Hydrogen atom abstraction from Bu_3SnH is the next step and should lead to **4** and/or **5.** The relative amounts of these **E, Z** isomers should be the same irrespective of whether **2** or **3** is used as the actual amounts produced is determined by the relative energies of the transition states leading to **4** and **5**[2]. Apparently formation of **5** is disfavoured and hence **4** was the sole isolable product obtained in the reaction of both **2** and **3** with low concentration of Bu_3SnH (0.07 M). The yield was 85% and 73% from **2** and **3** respectively. A most unexpected result was obtained when a high concentration (2.4 M) of the reagent was used[7]. Whereas the iodide **2** gave only the **E** isomer **4** in 70% yield, the xanthate **3** gave a 60% yield of a mixture of **Z** and **E** isomers with the former predominating. The ratio of **5:4** was 7:3. Any explanation for the "reversal of sterochemistry" on using the xanthate must take into account that the same xanthate gave exclusively the **E** isomer **4** when a low concentration of Bu_3SnH was used.

A reasonable explanation is that an intramolecular hydrogen atom abstraction leading to the **Z** isomer intervenes in the case where "reversal" is observed. Fortunately Barton[4] had obtained hemithioacetals in the reaction of xanthates with Bu_3SnH. According to him the diversion to these from fragmentation to alkyl radical is due to the reaction of its immediate precursor with additional molecules of Bu_3SnH. The path proposed by him for formation of a thioformate intermediate is followed in **Scheme 2**. We propose that the radical formed by attack of $Bu_3Sn^{\bullet}$ on the thioformate **8**, takes part in a concerted reaction which involves fragmentation, cyclisation and intramolecular hydrogen atom abstraction by a vinyl radical.



Scheme - 2

The methoxy group is not the primary cause of the "reversal". Thus the desmethoxy analogue of **2** gives the desmethoxy analogues of **4** and **5** in the ratio of 70:30 with Bu_3SnH (2.4 M) while with the desmethoxy analogue of **3** a "reversal" to a ratio of 43:57 results under the same conditions.

REFERENCES AND NOTES

1. All communications should be sent to SKP at A/32, Bldg.No.11, Jankalyan Nagar, Malad (West), Bombay 400 095, India.
2. Pradhan S. K. and Patil G. S. *Tetrahedron Letters* **1989**, 30, 2999.
3. Eschenmoser fragmentation of 16α,17α -epoxy-21-methoxypregn-5-en-20-one followed by $NaBH_4$ reduction gave **1**. Conversion of **1** to **2** was via mesylate. For preparation of **3**, **1** was successively treated with NaH, CS_2 and CH_3I. All compounds including **4**, **5** and **6** were fully characterised with spectral data in complete agreement. Chemical shifts of C-18 methyls in ^1H nmr of **4** and **5** were used for assigning the **E** and **Z** configurations resp. See ref. 2.
4. Barton D.H.R., Crich D., Lobberding A. and Zard S.Z. *J. Chem. Soc., Chem. Commun.*, **1985**, 646.
5. Curran D.P. and Kim D., *Tetrahedron* **1991**, 47, 6171.
6. If cyclisation of **2** occurs via iodine atom transfer the vinyl iodide formed should generate the same mixture of vinyl radicals on reaction with Bu_3SnH.
7. All reactions of **2** and **3** were catalysed by AIBN and involved 6 hr. reflux in benzene. As expected **6** was formed at high [Bu_3SnH]. Its yield was 7% and 18% respectively from **2** and **3**.

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