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A Novel synthesis of Steroidal Halomethylenes and Their Ring Opening Reaction to Alkynes

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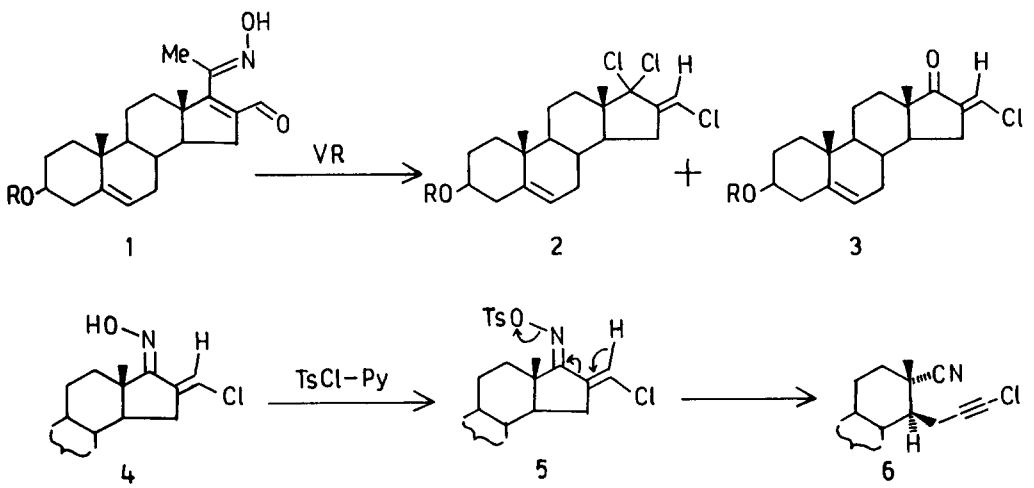
Abstract : γ-Formyl conjugated steroidal oximes under Vilsmeier condition afforded (E)-chloromethylene as potential precursor of steroidal alkynes via D-ring cleavage.

Recently, halomethylenes attract considerable attention as promising tools in organic synthesis[1]. The development of new methods for their synthesis is of continued interests because these are ideal templates for broad range of compounds via exchange of organometallic compounds[2] and heterocyclisations[3]. In general, their preparations are accomplished by photolytic carbene insertion[4], condensation and enolization of activated cyclic ketones[5] and ring expansion of alkynyl cyclopentanols[6]. Enediynes are well known class of antitumor antibiotics bearing an unusual diene-diyne moiety responsible for duplex DNA cleavage[7]. Despite structural complexities the synthesis of enediynes is achieved by alkyne side chain elongation and cyclisation[8]. The steroidal D-ring offers remarkable scope for molecular manipulation[9], however, the synthesis of steroidal enediyne is yet a fascinating synthetic goal. Our continued interests in the chemistry of aza compounds[10] has shown steroidal azadienes as potential organic synthones[11]. Here, in this communication we report a novel method for stereoselective synthesis of steroidal (E)-chloro methylenes from γ-formyl conjugated oximes and their utility for ring opening reaction to chloroalkynes.



	a	b	c
R	$COCH_3$	CHO	H

The reaction of one molar equivalent of 3-acetoxy-16-formyl-5,16-dehydropregnenolone-20-oxime (1a)[11] with an excess of Vilsmeier reagent[12] afforded unexpectedly 17,17-dichloro-androst-16(E)-chloromethylene (2a) and 16-(E)-

chloro methylene-epiandrosterone (3a) respectively in 72% and 10% yields. Treatment of hydroxylamine hydrochloride with 2a and 3a afforded 17-0xime (4a) which under the influence of TsCl-Pyridine accomplished bifunctional des-D-steroid (6a) in 54% yield[13]. The formation of 2a from 1a is believed to proceed by Beckmann rearrangement followed by the nucleophilic attack of the chloride ion on tautomerized imine bond at C-17 and 3a is formed by hydrolysis of 2a during work-up. The failure of reaction of 2a and 3a with hydroxylamine to yield isoxazole indicates trans stereochemistry of 16-chloromethylene group which is further supported by NMR signals[14] of the vinylic protons at δ6.40 and δ6.86 respectively. The formation of the compound 6a bearing a nitrile and chloropropyne group is the result of D-ring cleavage at C_{16}-C_{17} of 5a due to TsOH elimination and rearrangement.

In conclusion we have observed that chloromethyleneiminium salt efficiently convert steroidal γ-formyl conjugated oximes to (E)-chloromethylenes as convenient precursor to des-D-steroidal alkynes and rendered a novel strategy for the precursor of a novel class of steroidal enediynes. Further work on steroidal alkynes are in progress.

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13. Compound **2a** : m.p. 170-71°C ($CHCl_3$); IR (KBr) : ν_{max} 2950, 1735 cm^{-1}; ^{1}HNMR($CDCl_3$) : δ 6.40(1H, s), 5.20(1H, bs),4.35(1H, m), 1.85(3H,s), 0.95(3H,s), 0.80(3H,s), 2.30-1.10(17H,m) ; MS m/z 370(M^+-CH_3COOH, 98%), 372[(M^++2)- CH_3COOH, 100%], 374[(M^++4)-CH_3COOH, 33%]. **3a** : m.p. 155-56°C ($CHCl_3$); IR(KBr) ν_{max} 2945,1740, 1700 cm^{-1}; ^{1}HNMR($CDCl_3$) : δ 6.86(1H, t, J=2Hz), 5.15(1H, bs), 4.30(1H, m), 1.90(3H,s), 0.85(3H,s), 2.30-1.10(17H,m); MS m/z 316(M^+-CH_3COOH,100%), 318[(M^++2)-CH_3COOH, 33%]. **6a** : m.p.166-67°C; IR(KBr) ν_{max} 2940, 2220, 1740, 1590 cm^{-1}; ^{1}HNMR ($CDCl_3$) : δ 5.20(1H, bs), 4.35(1H,m), 1.95(3H,s), 1.90(3H,s), 1.15- 3.35(17H,m); MS m/z 313 (M^+- CH_3COOH, 100%), 315[(M^++2)-CH_3COOH, 33%].
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