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The First Synthesis of an A-Ring Fused Steroidal Isothiazole

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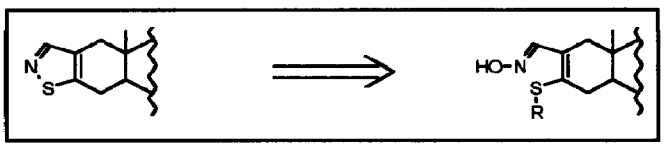
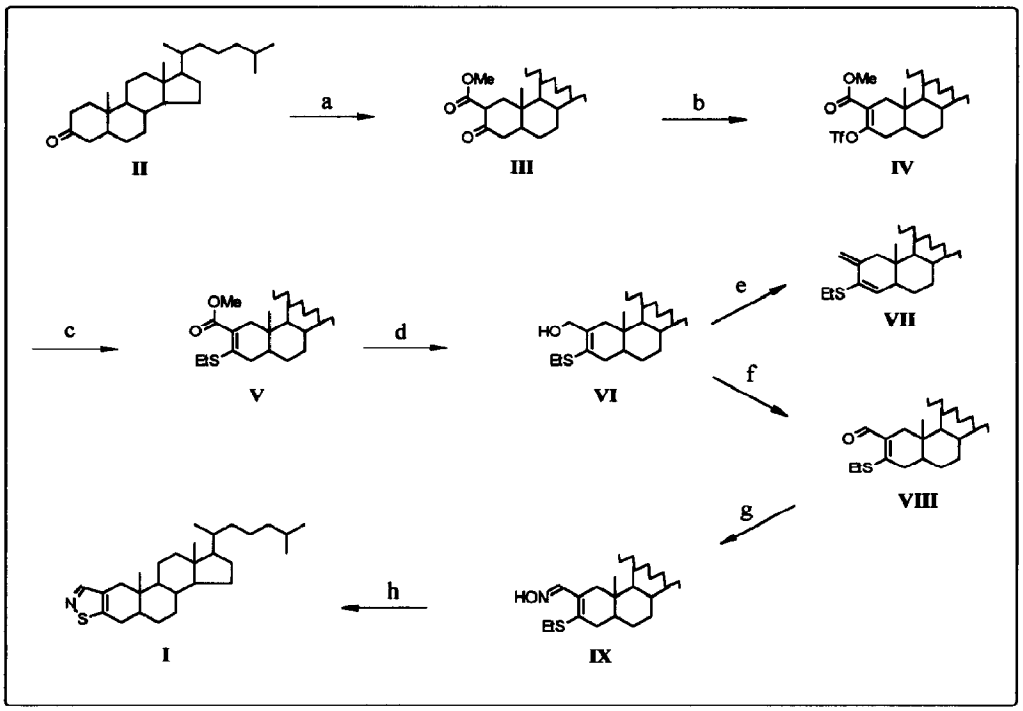
Abstract: A simple and efficient route to A-ring fused steroidal isothiazoles was developed. The key step involves C-S bond formation via substitution of a vinyl triflate at C-3.

Prostate cancer is a common malignancy in the worldwide male population. Although hormonal therapies are commonly used, antiandrogens have shown to be as effective and less toxic.[1] Several pharmaceutical companies[2] are now focusing on the biological evaluation of synthetic steroidal antiandrogens. In this sense, the Food and Drug Administration has recently approved one of them (Proscar,[3] Merck & Co.) to be used. However many steroidal and nonsteroidal antiandrogens have other properties (compensatory increase in hormonal levels, progestational activity, inhibition of fertility)[4] that reduce their use for clinical therapies.

It was known that the electronic character of the heterocyclic ring is critical in the binding affinity[5] and responsible for the biological activity[6] of several heterocyclic fused steroids. Semiempirical and *ab initio* level calculations performed on a series of heterocycles indicated the requirement for a partial negative charge at the heteroatom attached to C-3 of the steroid nucleus to attain androgen receptor affinity. Synthesis and testing of some A-Ring fused steroids supported this hypothesis. In view of this, we decided to synthesize the isothiazol derivative I. Examination of the literature showed that a few methods have been developed for the preparation of mononuclear and aromatic isothiazoles[7] but no steroidal derivatives have been previously reported. Toward a [2,3-d] system an intramolecular cyclization of an aldoxime with a thioenolether should provide a convenient approach.





Scheme 1: (a) i. LICA, THF, -78°C; ii. HMPA; iii. $CNCO_2Me$, -78°C; (b) i. NaH, CH_2Cl_2; ii. Tf_2O; (c) EtSNa, EtSH; (d) DIBAL, toluene, -20°C; (e) Swern oxidation; (f) MnO_2, hexane, ultrasound; (g) $NH_2OH.HCl$, Py:EtOH 1:1; (h) Ac_2O, Py, reflux.

A vinyl triflate at C-3 was supposed to be a convenient intermediate for the regiospecific introduction of the C2-C3 unsaturation and C-S bond formation. The synthetic route to **I** is depicted in the **Scheme 1**.

The enolate at C-2 of 5α-cholestan-3-one (**II**) was initially quenched with $ClCO_2Et$ but the O-acylated product was exclusively isolated. Compound **III** was synthesized selectively using Mander's Reagent.[8] Treatment of **II** with LICA followed by addition of $CNCO_2Et$[9] afforded compound **III** in 70% yield.

The different oxidative degree of both oxygenated functions allowed the preferential enolization of the ketone fixing the final regiochemistry of the double bond. In order to obtain the thioenolether, a good leaving group at the vinylic position was necessary and vinyl triflates are known as good precursors of carbenium ions.[10] They were used in numerous synthetic transformations with stannanes and organocuprates reagents[11] in order to prepare alkyl substituted olefins (C-C bond), but nothing has been reported about its use for C-S bond formation. Reaction of compound **III** with sodium hydride in dichloromethane[12] at room temperature and subsequent

addition of triflic anhydride produced 2-carboxymethyl-3-trifluoromethansulfonyloxy-5α-cholest-2-eno (IV) in 75% yield. Compound IV was then mixed with sodium thioetoxide in thioethanol at room temperature to afford V in a smoothly and complete reaction (95% yield).[13]

Treatment of the ester derivative V with DIBAL (in a molar ratio steroid:DIBAL < 1 and -100°C) or with lithium aluminum hydride/diethyl amine complex[14] afforded in both cases the corresponding alcohol VI instead of the necessary aldehyde. Taking this into account, we decided to use a reduction-oxidation approach. Oxidation of VI was attempted by using Swern method[15] with freshly destilled oxalyl chloride but the dehydrated compound VII was isolated as an important by-product. A second approach involved treatment with PCC but the aldehyde was obtained in low yield with sulfur oxidation as an important side reaction. Finally, the allylic alcohol was oxidised selectively and with high yield using activated MnO_2 in hexane and ultrasonic irradiation[16] (80% yield).

Compound VIII was stirred with hydroxylamine chlorhydrate in pyridine-ethanol (1:1) at room temperature for 20 minutes and the oxime was isolated in 99% yield. The oxime IX (0.28 mmol) was refluxed with anhydrous pyridine (4 ml) and acetic anhydride (0.125 ml) for 5.5 hours.[17] In these conditions ring closure was obtained affording compound I in 70% yield.[18]

In conclusion, transformation of IV to V provides a simple approach to vinyl thioethers. Taking into account that a number of different vinyl triflates have been successfully used in C-C bond formation reactions,[11] and the high yield for this C-S bond formation, it is possible that this methodology should be suitable in order to prepare vinylic derivatives. We are currently working on the preparation of different steroidal isothiazoles with different substitution at C-17 in order to be used for biological assays.

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13. A solution of 2-carboxymethyl-3-trifluoromethansulfonyloxy-5α-cholest-2-eno (**IV**) (1.44 g, 2.51 mmol) in ethanethiol (40 ml) was added to a suspension of sodium thioethoxide (9.74 g, 116 mmol) in ethanethiol (34.5 ml). The reaction mixture was kept at room temperature for 15 hs. After dilution with ethyl acetate, the mixture was washed with 1N NaOH and water. The dried ($MgSO_4$) extract was evaporated and the residue was purified by flash chromatography to give pure thioenolether **V** (1.16 g, 95%).
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18. Compound **I** was characterized: m.p.: 109.5-110°C (from methanol); $[\alpha]_D$: +61.0° (c=1.3, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.69(3H,s,18-Me); 0.74(3H,s,19-Me); 0.87(6H,d,J=6.6 Hz, 26-Me y 27-Me); 0.92 (3H,d,J=6.4 Hz, 21-Me) ; 2.22 (1H,d,J=15.8 Hz, 1α-H); 2.44 (1H,ddd,J=17.6,11.1,2.0 Hz,4β-H); 2.78(1H,d,J=15.7 Hz,1β-H); 2.83(1H,dd,J=17.7,4.5 Hz,4α-H); 8,16(1H,s,2'-H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 11.6(C-19); 12.0(C-18); 18.7(C-21); 21.1(C-11); 22.5(C-26); 22.8(C-27); 23.8(C-23); 24.2(C-15); 27.8(C-4); 28.0(C-25); 28.2(C-16); 28.8(C-6); 31.6(C-7); 35.6(C-8); 35.8(C-10 y C-20); 36.2(C-22); 37.1(C-1); 39.5(C-24); 39.9(C-12); 42.4(C-13); 42.5(C-5); 53.7(C-9); 56.3(C-14 y C-17); 133.2(C-2); 157.3(C-3); 157.8(C-2').

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