Stereoselective Synthesis of Steroidal (6*R*)-Spiro-1′,3′,4′-Thiadiazolines†

J. Chem. Research (S), 1998, 824–825†

Shamsuzzaman,*[a] M. Aslam[b] and Anwar Salim[b]

[a]*Department of Chemistry, Aligarh Muslim University, Aligarh-202 002, India*
[b]*Department of Chemistry, Jamia Millia Islamia, New Delhi-110 025, India*

Acetylation of 5α-cholestan-6-one thiosemicarbazone **1**, and its 3β-acetoxy-**2** and 3β-chloro-**3** analogues with acetic anhydride and pyridine at 80 °C afford selectively the corresponding (6*R*)-spiro-1′,3′,4′-thiadiazolines **4–6** in high yields.

There have been some reports in the literature of the cyclization of different aliphatic and aromatic aldehyde and ketone thiosemicarbazones under acetylating conditions which give substituted 1,3,4-thiadiazolines and thiadiazoles.[1–7] These thiadiazolines have also been reported to be biologically active materials.[8–10]

Here we report a novel and convenient preparation of some substituted steroidal (6*R*)-spiro-$\Delta^{2'}$-1′,3′,4′-thiadiazolines in high yields by the acetylation of steroidal 6-ketone thiosemicarbazones[11] with acetic anhydride and pyridine at 80 °C. 100% conversion was observed on TLC which also showed formation of a single product.

The proposed mechanism (Scheme 1) for the formation of these steroidal thiadiazolines can be explained on the basis of the hard and soft acid and base principle;[2,12] the thiosemicarbazones cyclize to the substituted Δ^2-1,3,4-thiadiazolines.

It is proposed that there is a considerable amount of steric hindrance to ring-closure from one side of the ring at C-6 which might be explained on the basis that although the sulfur atom is more bulky than nitrogen the NAc group becomes more bulky than the sulfur atom during cyclization (Scheme 1). Thus the thiadiazoline ring closes at C-6, by the attack of sulfur (being a better nucleophile) of the thiosemicarbazone moiety, preferentially from the front (β, axial) so that the bulky (NAc) group has an equatorial orientation giving minimum steric hindrance and maximum stability. This is further supported by the fact that during cyclization the bulky (NAcNHCSNHAc) group already attached to C-6 is moved towards the back (α, equatorial) side to reduce the steric hindrance due to 1,3-diaxial interactions mainly due to the presence of the C10β-methyl group, and leaving the front (β, axial) side for the attack of nucleophile to close the thiadiazoline ring at C-6. Therefore the only product of this reaction, the thiadiazoline, has *R* stereochemistry at C-6.

The Dreiding models also suggest the attack of sulfur from the β-side which pushes the bulkier NAc group to the less hindered α-side. Therefore the formulation of the compound as 6*R* is preferred over its isomer (6*S*). On the basis of these models it is suggested that the same should also be kinetically favourable.

The structures of these steroidal 1′,3′,4′-thiadiazolines (**4**–**6**) have been established on the basis of their physical, analytical and spectral data (Table 1).

Experimental

IR spectra were recorded on a Perkin Elmer 782 infrared spectrometer and ^{1}H NMR in $CDCl_3$ on a Bruker BZH-200 instrument with Me_4Si as internal standard.

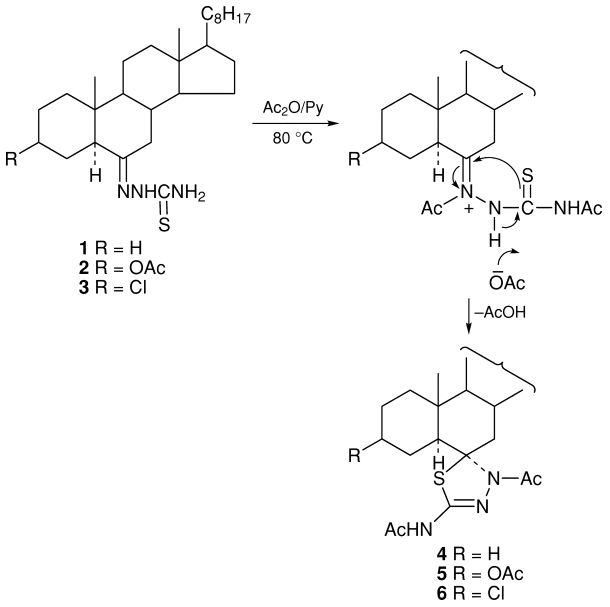
Table 1 Physical, analytical and spectral data of compounds **4–6**

Compound	Mp/°C	Yield (%)	IR (KBr, Neat or Nujol) ν_{max} cm^{-1}	^{1}H NMR ($CDCl_3$, Me_4Si) δ_H (ppm, 200 MHz)	Mass *m/z*
4	Semi-solid	88	3430, 3270(NH) 1710, 1680 (amide), 1640 (C=N)	11.70 m (s, 1H, N*H*Ac), 2.35 (s, 3H, NHCOC*H*$_3$), 2.17 (s, 3H, COC*H*$_3$), 1.12 (s, 3H, C10-C*H*$_3$), 0.66 (s, 3H, C13-C*H*$_3$), 0.91, 0.84 (other methyl protons)	M$^+$ 543, 501 (M – CH_2CO), 500 (M – Ac), 485 (M – NHAc), 459 (M – AcNHCN), 427 (M – SCNHAcN), 402 (M – AcNNCNHAc)
5	110	95	3415, 3260 (NH), 1730 (OAc), 1705, 1680 (amide)	11.30 (s, 1H, N*H*Ac) 4.9 (m, 1H, $W_{1/2}$ 18 Hz, axial, C3α-*H*), 2.27, 2.17, 2.05 (each s, 3H, Ac), 1.17 (s, 3H, C10-C*H*$_3$), 0.69 (s, 3H, C13-C*H*$_3$), 0.97, 0.87 (other methyl protons)	M$^+$ 601, 559 (M – CH_2CO), 558 (M – Ac), 553 (M – NHAc), 542 (M – OAc), 541 (M – AcOH), 517 (M – AcNHCN), 485 (M – SCNHAcN), 457 (541 – AcNHCN), 400 (541 – AcNNCNHAc)
6	Oil	92	3400, 3270 (NH), 1710, 1685 (amide), 1648 (C=N), 715 (C–Cl)	11.50 (s, 1H, N*H*Ac), 4.05 (m, 1H, $W_{1/2}$ 15 Hz, axial, C3 α-*H*), 2.31, 2.19 (each s, 3H, Ac), 1.14 (s, 3H, C10-C*H*$_3$), 0.71 (s, 3H, C13-C*H*$_3$), 0.91, 0.81 (other methyl protons)	M$^+$ 577/579, 534/536 (M – Ac), 519/521 (M – NHAc), 541 (M – HCl), 493/495 (M – AcNHCN), 461/463 (M – SCNHAcN), 457 (541 – AcNHCN), 400 (541 – AcNNCNHAc)

*To receive any correspondence.
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Oxidative Cyclization of Steriodal 6*-Ketone Thiosemicarbazones* **1**–**3**. *Steroidal* 6*R-Spiro*-1′,3′,4′*-thiadiazolines*

General Procedure.—Steroidal thiosemicarbazones **1**–**3** (1.0 mmol) were dissolved in chloroform (25 ml) and treated with freshly



Scheme 1

distilled acetic anhydride (11.0 mmol) and pyridine (2.5 mmol) and the mixture was stirred for 3–4 h over an oil bath at 80 °C. Reaction progress was monitored by TLC. After completion, the reaction solvents were removed under reduced pressure and the residue was purified by column chromatography over silica gel column (light petroleum–diethyl ether, 11:1) to give the respective steroidal (6*R*)-spiro-1′,3′,4′-thiadiazolines **4**–**6** (Table 1).

Thus the above method is useful for the stereoselective synthesis of the title compounds.

We are grateful to the late Professor M. S. Ahmad for useful discussion.

Received, 14th April 1998; Accepted, 1st September 1998
Paper E/8/02758G

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