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Note

Synthesis and characterization of steroidal 5′-formyl [6,7-*c*] pyrazoles using Vilsmeier-Haack reagent

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The preparation of hitherto unknown steroidal heterocycles containing pyrazole moiety fused to 6,7-position of the steroidal nucleus is described. These heterocycles have been prepared by the action of Vilsmeier reagent with steroidal tosylhydrazone in DMF. The structures of the compounds have been established on the basis of their elemental analysis and spectral data. A general mechanistic scheme for these reactions is also suggested based on current and previous results.

Keywords: Steroidal tosylhydrazone, heterocycles, Vilsmeier-Haack reagent, pyrazoles

As a part of the continuing interest towards the synthesis of modified steroids[1], which are expected to be biologically active, the fusion of heterocycles to steroids often lead to a change in physiological activities or appearances of new interesting biological behaviour. Thus, several steroidal heterocycles have been obtained exhibiting potential activity to inhibit cytochrome P450 enzyme aromatage, and their subsequent clinical application in the treatment of estrogen dependent breast cancer[2,3].

Pyrazoles constitute a class of compounds associated with wide spread application in the field of medicine[4-6] and agrochemistry[7], as evident from a large number of reports covering their preparation and uses. Many of these, such as steroidal pyrazoles, were found to possess antimicrobial, anti-inflammatory, hypotensive, hypocholesterolemic and diuretic activities[8-16]. The therapeutic importance of these steroidal pyrazoles[17] and study of reaction of DMF-$POCl_3$ which has dual role of reagent as well as solvent[18], with simple tosylhydrazones giving pyrazoles encouraged similar studies with steroidal tosylhydrazones.

Result and Discussion

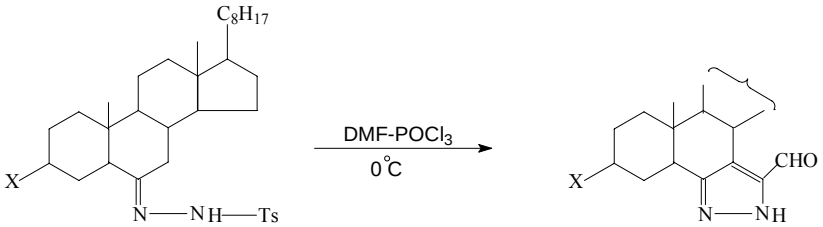
Easily accessible steroidal tosylhydrazones **1-3** were synthesized by literature method[19]. The substrates used for initial studies are 5α-cholestan-6-one tosylhydrazone **1** (Ref. 19), 3β-acetoxy-5α-cholestan-6-one tosylhydrazone **2** (Ref. 19) and 3β-chloro-5α-cholestan-6-one tosylhydrazone **3** (Ref. 19). The tosylhydrazones **1-3** when allowed to react with $POCl_3$ in DMF under cold conditions afforded steroidal pyrazole derivatives **4-6** as shown in **Scheme I**. The products have been characterized on the basis of their elemental analysis and spectral (IR, ^1H and ^{13}C NMR) studies.

The elemental analysis of the compound **4** corresponds to the molecular formula $C_{29}H_{47}ON_2$. Its IR spectrum shows a band at 3404 cm^{-1} which could be assigned to NH group and another band at 1708 may be ascribed to -CHO and other important bands are exhibited at 1595, 1625, 1378 cm^{-1} for (C=N), (C=C) and (C-N). These values supported the presence of pyrazole moiety[20] at 6,7 position of ring B. The structure **4** is well supported by the ^1H NMR spectral study of the compound. NMR spectrum displayed a singlet at δ 8.09 indicating the presence of aldehyde, other prominent peaks were observed at δ 0.92, 0.85, 0.65 indicating the presence of angular and side chain methyl protons. The absence of any signal for aromatic protons in the NMR spectrum suggested the removal of tosyl group (**Scheme II**). The structure of compound **4** has been further supported by its mass spectrum ($M^{+\bullet}$ 439). On the basis of foregoing discussion and mechanism (**Scheme II**) proposed, this compound can be best characterized as 5′-formyl-5α-cholestan [6,7-*c*] pyrazole **4**. Structures of **5**, **6** were also assigned on the basis of similar data (**Tables I** and **II**). Moreover, the ^{13}C NMR carbon resonances of the compound **4** were assigned in support of its structure (**Table II**).

In the light of available mechanism[21,22] formation of **4** from **1** under the conditions can be shown according to **Scheme II**. This may be taken as tentative in the absence of studies to establish the mechanism of reaction.

Experimental Section

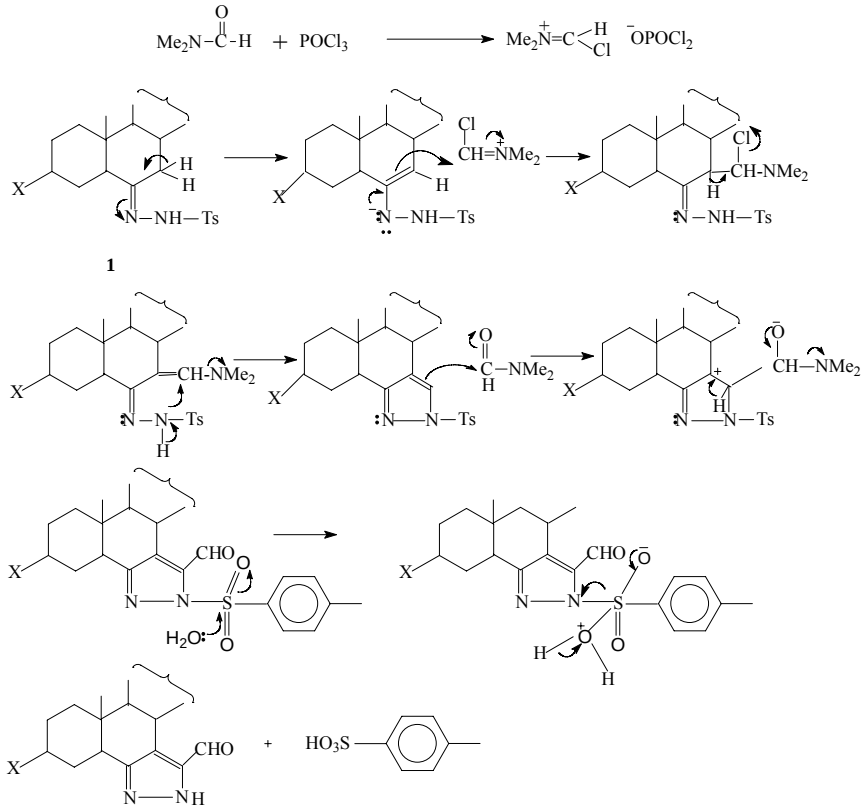
Melting points were determined on a Kofler apparatus and are uncorrected. The IR spectra were



1-3
1: X= H
2: X= AcO
3: X= Cl

4-6
4: X= H
5: X= AcO
6: X= Cl

Scheme I



1

4

Scheme II

recorded on KBr pellets with Pye Unicam SP3-100 spectrophotometer and its values are given in cm^{-1}. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ on a Jeol Eclipse (400 and 75 MHz) instrument with TMS as internal standard and its values are given in δ (ppm). Thin layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapours to check the homogeneity as well as to study the progress of reaction. Petroleum ether refers to a fraction of b.p. 60-80°C. Sodium sulphate (anhydrous) was used as a drying agent.

Representative procedure for the preparation of steroidal pyrazoles, 4-6

Steroidal tosylhydrazones **1-3** (0.5 g) in DMF (6 mL) were kept under ice-cold condition. $POCl_3$ (0.5 mL) was added with stirring at such a rate that the temperature of the reaction-mixture did not exceed 10°C. After complete addition, the reaction-mixture was allowed to attain RT and stirred for about 1 hr and the progress of the reaction was monitored by TLC. After ensuring the completion of reaction, the products were poured onto crushed ice and left

Table I — Physical and chemical characterization data of the compounds **4-6**

Compd	Compd	Yield (%)	m.p. (ºC)	Mol. Formula (Mol. wt.)	Found (Calcd)% C	H	N
4	5′-formyl-5α-cholestan [6,7-*c*] pyrazole	70	99	$C_{29}H_{47}N_2O$	79.45	10.50	6.39
				(M^+ • 439)	(79.27	10.70	6.37)
5	5′-formyl-3β-acetoxy-5α-cholestan [6,7-*c*] pyrazole	60	Semi- Solid	$C_{31}H_{49}N_2O_3$	75.0	9.67	5.64
				(M^+ 497)	(74.84	9.85	5.63)
6	5′-formyl-3β-chloro-5α-cholestan [6,7-*c*] pyrazole	55	Semi- Solid	$C_{29}H_{46}N_2ClO$	73.41	9.49	5.90
				(M^+ 474/472)	(73.38	9.46	5.87)

Table II — Spectral characterization data of the compounds **4-6**

Compd	^{1}H NMR ($CDCl_3$, 400MHz), (δ, ppm)	^{13}C NMR ($CDCl_3$, 75MHz), (δ, ppm)
4	8.8s (1H, NH), 8.09s (1H, CHO), 1.13s (3H, C_{10}-CH_3), 0.65s (3H, C_{13}-CH_3), 0.92, 0.85 (other side chain methyl protons)	C6 (140.16), C7 (129.12), C1′(152.41), CHO (212.84) C3 (25.20)
5	8.73s (1H, NH), 8.03s (1H, CHO), 4.6m (1H, C_3-αH, $W_{1/2}$ 16 Hz), 2.02s (3H, CH_3COO), 1.11s (3H, C_{10}-CH_3) 0.66s (3H, C_{13}-CH_3), 0.87, 0.75 (other methyl protons)	CH_3COO (171.61), C3 (72.41), C6 (136.41), C7 (128.7) C1′ (151.15), CHO (212)
6	8.7s (1H, NH), 8.10s (1H, CHO), 4.12m (1H, C_3-αH, $W_{1/2}$ 17 Hz), 1.13s (3H, C_{10}-CH_3) 0.66s (3H, C_{13}-CH_3), 0.87, 0.78 (other methyl protons)	C3 (59.16), C6 (138.2), C7 (120.2), C1′ (153.14), CHO (212)

overnight in a refrigerator. The orange yellow viscous precipitate thus obtained was filtered, washed with water, dried and purified by recrystallization from methanol to afford **4**, **5**, or **6**, (the products **5** and **6** failed to crystallize from suitable solvents). Yields, physical state, microanalytical and spectral data of the products are given in **Table I** and **II**.

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