A FACILE SYNTHESIS OF 6,7-FUSED STEROIDAL THIAZOLES VIA 1,3-INTRAMOLECULAR MIGRATION OF BROMINE/ALLYLIC DISPLACEMENT OF BROMINE

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(Received: February 25, 2008 - Accepted: September 11, 2008)

ABSTRACT

A facile synthesis of an array of 6,7-fused steroidal thiazoles (4-9) is reported. Replacement of lachrymatory 7-bromosteroidal ketones (4a) with readily accessible 5-bromosteroidal ketones (1-3), as a starting material, on simple condensation with thiourea or phenylthiourea gives the thiazole fused ring products. The products have been characterized on the basis of microanalytical and spectral data, which find support in some cases from comparison with previously known samples. A rationalization for the routes of conversion is given, based on current and previous results.

Keywords: Steroidal thiazoles, lachrymatory, phenylthiourea, IR spectroscopy.

INTRODUCTION

Thiazole is an important heterocycle found in various natural products, notably thiamine (vitamin B).¹ Therefore, thiazole derivatives have been isolated and synthesized in view of their pharmacological activities *viz* antibacterial, antifungal, anti-inflammatory and antiviral.²⁻⁶ These are also employed as antiallergic,⁷ anthelmintic⁸ and as sedative hypnotic agents.⁹ In addition, N-phenyl-1,3-thiazoles are expected to be important constituents of the medicines used for the treatment of multiple myeloma, chronic autoimmune disease, as well as AIDS.¹⁰ Due to the significance of thiazole derivatives in medicinal chemistry, considerable effort has been devoted to develop alternate routes for their synthesis.¹¹⁻²⁸

Although several strategies with variable yields have been reported for the synthesis of steroidal as well as non-steroidal thiazoles, the Hantzsch's protocol²⁹⁻³¹ continues to be a method of choice involving the reaction of α -halocarbonyl compound with an appropriate thiourea or thioamide. Thus, we have also selected the Hantzsch's protocol for this purpose, 5-bromosteroidal ketones,³²⁻³³ are selected instead of 7-bromosteroidal ketones because both lead to the same product but preparation of 7-bromocholestan-6-one²⁰⁻²¹ is much more tedious leading to a mixture of products.

The paper describes the synthesis of thiazoles by simple condensation reaction between steroidal- α -bromoketones and thiourea or phenylthiourea in methanol.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. The compounds mentioned in this paper are known and their full characterization data, except ¹³C NMR, have been previously reported in the literature. Confirmation of the compounds in our labs was done using, IR, ¹H NMR, ¹³C NMR, MS and elemental analysis as appropriate. The IR spectra were recorded on KBr pellets with Pye Unicam SP3-100 spectrophotometer and its values are given in cm⁻¹. Elemental analyses (C, H and N) were carried out with a Carlo Erba EA-1108 analyzer. ¹H-NMR spectra were run in CDCl₃ on a Bruker DRX-300 (300 MHz, FT-NMR) instrument with TMS as internal standard and its values are in ppm (δ). ¹³C NMR spectra were recorded on a Bruker Avance II 400 spectrometer in CDCl₃. Mass Spectra were measured on JMS-D300, AIE MS-9 spectrometer using direct insertion technique at a source temperature of 250 °C. Thin layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapors to check the purity as well as the progress of reaction. Petroleum benzene refers to a fraction of b.p. 60-80 °C. Sodium sulfate (anhydrous) was used as a drying organic extracts after reaction work-up. All the solvents were distilled before use.

Synthesis of steroidal thiazoles (Representing procedure)

To a solution of 5-bromosteroidal ketone (1, 2 or 3) (1 mmol) in methanol (10 mL) was added thiourea or phenylthiourea (1 mmol) and the mixture was heated under reflux for 10 hrs. After completion of reaction, as determined by TLC, the reaction mixture was diluted with water and extracted thoroughly with ether. The extracts were washed successively with water and dried over anhydrous sodium sulfate (Na₂SO₄), and concentrated to yield the steroidal thiazole (4, 5, 6, 7, 8 or 9) as oil, which were crystallized from low fraction benzene (petroleum benzene) to obtain pure products. The results are given in table 1 and 2.

RESULTS AND DISCUSSION

The easily accessible steroidal 5-bromoketones (1, 2, and 3) were synthesized by a procedure described in the literature.³²⁻³⁵ A condensation reaction involving bromoketones and thiourea or phenylthiourea in methanol under reflux and subsequent processing leads to the formation of steroidal thiazoles having thiazole moiety at 6,7 position of ring B of cholestane skeleton. (4-9). The advantage of the reaction is to evade the lachrymatory 7-bromoketone (4a), as a starting material. The striking feature of the reaction is either 1,3-intramolecular shift of bromine³² or allylic displacement of bromine during the formation of desired products. The reaction of 3 β -acetoxy-5-bromo-6-oxo-5 α -cholestane (1)³², 3 β -propanoyloxy-5-bromo-6-oxo-5 α -cholestane (2)³³ and 5-bromo-6-oxo-5 α -cholestane (3),³⁴⁻³⁵ with thiourea or phenylthiourea in methanol under reflux for about 8-10 hours afforded 3 β -acetoxy-2'-amino-5 α -cholestan-6-eno[6,7-*d*] thiazole (4)²⁰⁻²¹ or 3 β -acetoxy-2'-N-phenylamino-5 α -cholestan-6-eno[6,7-*d*] thiazole (7) and its series compounds (5, 8) and (6, 9), respectively, (Scheme 1), in moderate yields.

Scheme1. Synthesis of fused steroidal thiazoles

The structure of compound (4) was established by IR, ¹H NMR, ¹³C NMR, MS and microanalytical data. Compound (4) gave diagnostic IR bands at 3240 cm⁻¹ (-NH₂), 1730 and 1265 cm⁻¹ (CH₃COO-), 1630 cm⁻¹ (C=C) and 1540 cm⁻¹ (C=N).³⁶ Some other bands were also observed at 1320 cm⁻¹ for (C-N) and 665 cm⁻¹ for (C-S)³⁶ stretching frequencies supporting the presence of the thiazole moiety. The ¹H NMR spectrum exhibited a broad singlet at δ 5.31 integrating for two protons corresponding to the -NH₂ group and another broad peak appeared at δ 4.93 for C₅- α H. A multiplet was observed, integrating for one proton at δ 4.71 (W_{1/2}=17 Hz), which could be attributed to the C3- α H, axial proton (A/B ring junction trans).³⁷ The methyl protons of the acetate group appeared at δ 2.10 as a sharp singlet. However, the angular methyl protons (C₁₀-CH₃), (C₁₃-CH₃) as singlets and side chain methyl protons (C₂₁-CH₃), (C₂₅-(CH₃)₂) as doublets, were observed at δ 1.21, 0.92, 0.81 and 0.67 respectively. In the ¹³C NMR spectrum, the peak appearing in the range of δ 162-166 ppm corresponds to C-2' of the thiazole ring and other characteristic ¹³C NMR signals appeared at δ 170.67

(CH₃COO), 149.01 (C-6) and 122.75 (C-7) respectively (Fig. 2). The absence of a carbonyl as well as an α -bromo group absorption at 1710 (C=O) and 780 (C...Br) cm⁻¹ confirms the formation of (4). Thus, the above data supports the formation of 3 β -acetoxy-2'-amino-5 α -cholestan-6-eno [6,7-*d*] thiazole (4). The identity of 4, was further supported by m.p., mixed m.p., (reported, m.p., 202 °C) and co-tlc.²⁰⁻²¹ The products (5-9) were also characterized on the basis of similar accounts. Besides the ¹³C NMR data (The structure elucidation of 4-9 is mainly based on ¹³C NMR spectroscopy see Experimental for details) and elemental analysis, the appearance of the molecular ion peak at *m/z* 500 (M⁺) is in good agreement with the molecular formula C₃₀H₄₈N₂O₂S (4) which further establishes its formation (Fig. 1). Ahmad³⁸ has reported a similar set of title compounds starting from the same material but with a different solvent, methanol but provided no satisfactory mechanism. However, Shamsuzzaman *et al.*³⁹ reported different steroidal thiazoles starting from similar precursor using ethanol as a solvent with a refluxing period of 2-3 hrs.

Fig. 1 Fragmentation pattern of compound 4

Fig. 2. ¹³C NMR spectrum of compound 4 in CDCl₃

The effect of solvent in synthesis of thiazoles could not be ruled out. The study of solvent effects as well as reaction conditions⁴⁰ in the synthesis of thiazoles is in progress for future reports. The formation of product (4) can be explained considering that during the reaction, 1,3 shift of bromine³² from C5 to C7 leads to the formation of intermediate 4a *in situ* (scheme 3), followed by S_N² attack of sulfur of the reagent and subsequent cyclization, which gives the product (4). The formation of steroidal thiazole could also be explained by an alternate route, considering that during the reaction, allylic displacement of bromine and subsequent attack of sulfur atom of reagent followed by cyclization, leading to the formation of the desired product (4). It is expected that driving force to accelerate reaction towards product direction is an enol tautomeric form as established by ¹H NMR spectroscopy in similar case of

thiazoles.⁴¹ The tentative mechanism, explaining the observed products (5-9), has been proposed on the basis of spectral studies as well as current and previous results.⁴²

Scheme-2. Allylic displacement of bromine by the attack of sulfur atom of reagent

Scheme-3. 1,3-shift of bromine followed by S_N² attack of Sulfur atom of reagent

CONCLUSION

The present work describes a facile synthesis of steroidal thiazoles starting from conveniently accessible precursor 5-bromosteroidal ketones instead of lachrymatory 7-bromosteroidal ketones. The reported compounds can serve as biologically relevant compounds as their analogs were found to possess versatile anti-inflammatory and anti-tuberculosis activities.

Table 1. Characterization data of the compounds (**4** to **9**).

Compound	Name	Yield (%)	M.p. (°C)	Molecular formula (mol. wt)	Found (Calculated) (%)			
					C	H	N	S
4	3β-acetoxy-2'-amino-5α-cholest-6-eno [6,7- <i>d</i>]thiazole	60	200-202 (202) ²⁰⁻²¹	C ₃₀ H ₄₈ N ₂ O ₂ S (500)	71.84 (72.0)	9.47 (9.60)	5.71 (5.60)	6.21 (6.40)
5	3β-propanoyloxy-2'-amino-5α-cholest-eno [6,7- <i>d</i>]thiazole	55	119	C ₃₁ H ₅₀ N ₂ O ₂ S (514)	72.12 (72.37)	9.68 (9.72)	5.51 (5.44)	6.18 (6.22)
6	2'-amino-5α-cholest-6-eno [6,7- <i>d</i>]thiazole	58	185-187 (187) ²⁰⁻²¹	C ₂₈ H ₄₆ N ₂ S (442)	75.88 (76.01)	10.17 (10.40)	6.40 (6.33)	7.08 (7.23)
7	3β-acetoxy-2'- <i>N</i> -phenylamino-5α-cholest-6-eno [6,7- <i>d</i>]thiazole	50	121	C ₃₆ H ₅₂ N ₂ O ₂ S (576)	74.89 (75.00)	8.92 (9.03)	4.95 (4.86)	5.48 (5.55)
8	3β-propanoyloxy-2'- <i>N</i> -phenylamino-5α-cholest-6-eno[6,7- <i>d</i>]thiazole	53	140	C ₃₇ H ₅₄ N ₂ O ₂ S (590)	74.93 (75.25)	8.82 (9.15)	4.80 (4.74)	5.50 (5.42)
9	2'- <i>N</i> -phenylamino-5α-cholest-6-eno [6,7- <i>d</i>]thiazole	55	132	C ₃₄ H ₅₀ N ₂ S (518)	78.55 (78.76)	9.51 (9.65)	5.59 (5.40)	5.93 (6.17)

Table 2. Spectral data of the compounds (**4** to **9**)

Compound	IR (KBr) cm ⁻¹	¹ HNMR (CDCl ₃) (δ, ppm)	MS: m/z
4	3240 (-NH ₂), 1730, 1265 (CH ₃ COO), 1630 (C=C), 540 (C=N), 1320 (C-N) and 650 (C-S).	5.3 (brs, 2H, -NH ₂ exchangeable with deuterium), 4.93 (brs, 1H, C ₅ -αH), 4.71 (m, 1H, W _{1/2} =18 Hz, C _{3α} -H), 2.05 (s, 3H, CH ₃ COO-), 1.21 (s, 3H, C ₁₀ -CH ₃), 0.67 (s, 3H, C ₁₃ -CH ₃), 0.92, 0.81 (other side chain methyl protons).	500 (M ⁺), 485 (M ⁺ -CH ₃), 387 (M ⁺ -C ₈ H ₁₇), 440 (M ⁺ -CH ₃ COOH), 425 (M ⁺ -CH ₃ COOH and CH ₃), 373 (M ⁺ -CH ₃ COOH, CH ₃ and CH ₂ N ₂), 398 (M ⁺ -CH ₃ COOH and CH ₂ N ₂) and 327 (M ⁺ -CH ₃ COOH and C ₈ H ₁₇).
5	3200 (-NH ₂), 1735, 1240 (CH ₃ CH ₂ COO), 1520 (C=N), 1450 (C-N) and 660 (C-S).	5.2 (brs, 2H, -NH ₂ exchangeable with deuterium), 4.81 (brs, 1H, C ₅ -αH), 4.9 (m, 1H, C _{3α} -H, W _{1/2} =18 Hz), 2.2 (q, 2H, CH ₃ CH ₂ COO, J=7 Hz), 1.21 (s, 3H, C ₁₀ -H ₃), 0.69 (s, 3H, C ₁₃ -CH ₃), 0.92, 0.81 (other side ethyl protons).	574 (M ⁺), 499 (M ⁺ -CH ₃), 401 (M ⁺ -C ₈ H ₁₇), 440 (M ⁺ -CH ₃ CH ₂ COOH), 327 (M ⁺ -CH ₃ CH ₂ COOH and C ₈ H ₁₇), 300 (M ⁺ -CH ₃ CH ₂ COOH and C ₁₀ H ₂₀), 386 (M ⁺ -CH ₃ CH ₂ COOH and C ₄ H ₆), 273 (M ⁺ -CH ₃ CH ₂ COOH, C ₄ H ₆ and C ₈ H ₁₇) and 231 (M ⁺ -CH ₃ CH ₂ CO OH, C ₄ H ₆ , C ₈ H ₁₇ and -NCNH ₂).
6	3250, 3150 (-NH ₂), 1625 (C=C), 1550 (C=N), 1470, 1370 (C-N) and 665 (C-S) ³⁵ .	5.3 (brs, 2H, -NH ₂ exchangeable with deuterium), 1.0, 0.92, 0.81 and 0.65 (other side chain methyl protons).	442 (M ⁺), 427 (M ⁺ -CH ₃), 400 (M ⁺ -CH ₂ N ₂), 386 (M ⁺ -C ₄ H ₈), 329 (M ⁺ -C ₈ H ₁₇), 302 (M ⁺ -C ₁₀ H ₂₀) and 301 (M ⁺ -H).
7	3000, 1600 (aromatic gp), 3200, 3150 (-NH), 1735, 1235 (CH ₃ COO), 1520 (C=N) and 650 (C-S).	7.4, 7.3 (5H, aromatic protons), 6.5 (brs, s, 1H, -NH), 3.8 (m, 1H, C _{3α} -H, W _{1/2} =16 Hz), 2.0 (CH ₃ COO), 1.02, 0.91, 0.81 and 0.70 (others methyl protons).	576 (M ⁺), 575 (M ⁺ -H), 484 (M ⁺ -NHPh), 499 (M ⁺ -Ph), 359 (M ⁺ -C ₈ H ₁₇ CH=CH ₂), 561 (M ⁺ -CH ₃), 463 (M ⁺ -C ₈ H ₁₇), 436 (M ⁺ -C ₁₀ H ₂₀) and 516 (M ⁺ -CH ₃ CO OH).
8	3000, 1600 (aromatic gp), 3200 (-NH), 1735, 1210 (CH ₃ CH ₂ COO), 1520 (C=N) and 660 (C-S).	7.4, 7.3 (m, 5H aromatic protons), 4.9 (m, 1H, C _{3α} -H, W _{1/2} =18 Hz), 6.1 (brs, 1H, -NH), 2.3 (q, CH ₃ CH ₂ COO, J=7 Hz), 1.30, 1.18, 0.96 and 0.68 (other methyl protons).	590 (M ⁺), 477 (M ⁺ -C ₈ H ₁₇), 575 (M ⁺ -CH ₃), 589 (M ⁺ -H), 498 (M ⁺ -NHPh), 516 (M ⁺ -CH ₃ CH ₂ COOH) and 450 (M ⁺ -C ₁₀ H ₂₀).
9	3010, 1600 (aromatic gp), 3240 (-NH), 1530 (C=N), 1320 (C-N) and 600 (C-S).	7.4, 7.3 (m, 5H, aromatic protons), 6.6 (brs, 1H, -NH exchangeable with deuterium), 1.12, 0.91, 0.85, and 0.65 (other methyl protons).	518 (M ⁺), 517 (M ⁺ -H), 503 (M ⁺ -CH ₃), 462 (M ⁺ -C ₄ H ₈), 461 (M ⁺ -C ₄ H ₈ and H), 441 (M ⁺ -Ph), 426 (M ⁺ -NHPh), 411 (M ⁺ -NHPh and CH ₃) and 503 (M ⁺ -CH ₃).

¹³C NMR (CDCl₃) (δ, ppm) (**4**); 170.67 (CH₃COO-), 162.91 (C-2'), 149.01 (C-6), 122.75 (C-7), 74.08 (C-3), 56.76 (C-14), 56.19 (C-17), 50.09 (C-9), 42.93 (C-13), 39.80 (C-5), 39.60 (C-12), 38.20 (C-8), 37.07 (C-1), 36.67 (C-20), 36.26 (C-22), 35.89 (C-10), 31.98 (C-4), 28.33 (C-16), 28.11 (C-24), 27.85 (C-2)*, 24.37 (C-23), 23.91 (C-15), 22.93 (C-25)*, 22.66 (C-11/C-27), 21.56 (C-19), 21.11 (CH₃COO-), 19.41 (C-26), 18.80 (C-21) and 11.95 (C-18). Asterisks denote assignments that may be interchanged; (**5**); 170.69 (CH₃CH₂COO-), 164.91 (C-2'), 149.61 (C-6), 123.25 (C-7), 73.18 (C-3), 27.71, 9.21 (CH₃CH₂COO-); (**6**); 163.50 (C-2'), 149.35 (C-6), 122.35 (C-7), 33.50 (C-1), 20.61 (C-2)*, 20.78 (C-3)*, 33.17 (C-4), 47.18 (C-5); (**7**); 170.67 (CH₃COO-), 165.91 (C-2'), 149.41 (C-6), 140.75, 128.99, 124.66, 121.89 (aromatic gp), 122.89 (C-7), 74.07 (C-3), 21.11 (CH₃COO-); (**8**); 170.67 (CH₃COO-), 165.91 (C-2'), 149.41 (C-6), 140.75, 128.99, 124.66, 121.89 (aromatic gp), 122.89 (C-7), 74.07 (C-3), 21.11 (CH₃COO-); (**9**); 162.89 (C-2'), 149.31 (C-6), 138.82, 128.98, 121.89, 117.91 (aromatic gp), 123.01 (C-7), 20.61 (C-2), 20.78 (C-3), 33.17 (C-4), 47.18 (C-5) and for other signals (¹³CNMR) are in close accord with the cholestane series.

ACKNOWLEDGEMENT

We thank the Chairman, Department of Chemistry, A.M.U., Aligarh, for providing necessary research facilities. We wish to thank Professor M. Mushfiq for helpful discussions and his interest in our work. We are grateful to the SAIF, Panjab University for providing IR, ¹H NMR, ¹³C NMR and elemental analysis

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