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Synthesis of novel 16-spiro steroids: Spiro-7′-(aryl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazolo-*trans*-androsterone hybrid heterocycles

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ABSTRACT

The 1,3-dipolar cycloaddition of azomethine ylide derived *in situ* from the reaction of acenaphthylene-1,2-dione and 1,3-thiazolane-4-carboxylic acid to various exocyclic dipolarophiles synthesized from *trans*-androsterone and *trans*-dehydroandrosterone afforded a library of novel spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-(7′-aryl)-tetrahydro-1*H*-pyrrolo [1,2-*c*][1,3]thiazolo-*trans*-androsterone/dehydroandrosterone hybrid heterocycles respectively. These reactions proceeded stereo-specifically affording a single isomer of the 16-spiro steroids in excellent yields.

1. Introduction

Steroids are extensively available in nature and are well known for their profound biological activities and use in traditional medicines [1]. Syntheses of several modified steroids have received considerable attention in the recent years. In particular, the syntheses of new compounds comprising heterocyclic rings either fused or linked to the steroid framework have gained much importance [2]. Apart from being synthons for further modifications into more complex molecules, these steroidal heterocycles have been reported to possess a wide range of biological activities [2].

Spiro steroids are important class of compounds that are frequently found in nature, such as spirostanes, which include a spiroacetal moiety in the structure and show significant biological activities [3]. Generally, spiro compounds constitute a vital group of many naturally occurring compounds identified by their highly noticeable biological activities [4]. For example, coerulescine, horsfiline and elacomine exhibit anti tumor activity [5], whereas rynchophylline and corynoxeine are used in traditional Chinese medicine for the treatment of neurological and cardiovascular diseases, respectively [6]. The pentacyclic spirotryprostatin A and B compounds were shown to inhibit the growth of human chronic myelogenous leukemia K562 cells and human promyelocytic leukemia HL-60 cells [7].

The best studied spiro steroids are those which contain a spiro heterocyclic ring at C-17 [8], whereas the reports on the synthesis of C-16 spiro heterocyclic steroids are scarce [9]. The known C-16 spiro steroids are the cycloalkano derivatives [10], dioxaphosphorinanes [11], pyrazolines [12] and pyrrolidines [13]. In this context, we herein report the synthesis of novel C-16 spiro pyrrolo[1,2-*c*][1,3]thiazole containing *trans*-androsterone and *trans*-dehydroandrosterone hybrid heterocycles *via* 1,3-dipolar cycloaddition reactions. It is pertinent to note that the compounds with spiro pyrrolo[1,2-*c*][1,3]thiazole substructure are known to exhibit acetylcholinesterase (AChE) inhibition [14] and anti-tubercular activities [15]. Several methods have been devised to construct such bio-important spiro heterocycles of which 1,3-dipolar cycloaddition represents the widely investigated one [16]. In particular, the 1,3-dipolar cycloaddition of azomethine ylides to exocyclic olefins offers a versatile protocol for the synthesis of poly-functionalized spiro pyrrolo[1,2-*c*][1,3]thiazoles [14,15].

2. Experimental

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Elemental analyses were performed on a Perkin Elmer 2400 Series

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II Elemental CHNS analyzer. IR spectra were recorded in a Shimadzu FTIR-8400S using KBr pellet. The single crystal X-ray data set for **2k** and **3i** were collected on Bruker Kappa APPEXII diffractometer with Mo–K_α (λ = 0.71073 Å) radiation. SHELXTL software was used for structure solution and refinement. Silica gel-G plates (Merck) were used for tlc analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. All the chemicals were purchased from Aldrich and used without any further purification.

*2.1. General procedure for the synthesis of 16-(E)-arylidene-trans-androsterones **2** and 16-(E)-arylidene-trans-dehydroandrosterones **5***

A mixture of *trans*-androsterone **1** or *trans*-dehydroandrosterone **4** (1 mmol) and aromatic aldehyde (1 mmol) was dissolved in ethanol (5 mL) to which an alcoholic solution of potassium hydroxide (10%) was added drop wise. The mixture was allowed to stir for 60 min at ambient temperature and the progress of the reaction monitored by TLC intermittently. After completion of the reaction, the precipitated solid was filtered and washed with ethanol (10 mL) to afford the product **2** or **5** as colorless solid.

*2.1.1. (E)-16-(2-Methylphenyl)methylidene-trans-androsterone (**2h**)*

Obtained as white solid; Yield 97%; m.p. 180–182 °C; ^{1}H NMR 0.72–0.76 (m, 1H), 0.86 (s, 3H), 0.97 (s, 3H), 0.93–1.04 (m, 2H), 1.13–1.47 (m, 8H), 1.56–1.95 (m, 8H), 2.41 (s, 3H), 2.33–2.43 (m, 1H), 2.74 (dd, *J* = 15.9, 6.3 Hz, 1H), 3.58 (m, 1H), 7.22–7.24 (m, 3H), 7.44–7.46 (m, 1H), 7.65 (s, 1H). ^{13}C NMR 12.4, 14.5, 20.0, 20.6, 28.4, 29.2, 31.1, 31.4, 31.7, 34.7, 35.7, 36.9, 38.0, 44.9, 47.9, 49.7, 54.5, 71.1, 125.8, 128.6, 129.0, 130.6, 130.7, 134.4, 136.8, 138.7 and 209.8.

*2.1.2. (E)-16-(2-Methoxyphenyl)methylidene-trans-androsterone (**2i**)*

Obtained as white solid; Yield 98%; m.p. 142–144 °C; ^{1}H NMR 0.71–0.76 (m, 1H), 0.86 (s, 3H), 0.95 (s, 3H), 0.96–1.03 (m, 1H), 1.15–1.42 (m, 7H), 1.60–1.94 (m, 8H), 2.34–2.44 (m, 1H), 2.77 (dd, *J* = 15.2, 5.5 Hz, 1H), 3.52–3.61 (m, 1H), 3.86 (s, 3H), 5.08 (brs, 2H), 6.89–7.00 (m, 2H), 7.31–7.50 (m, 2H), 7.84 (s, 1H). ^{13}C NMR 12.4, 14.5, 20.6, 28.4, 29.4, 31.1, 31.4, 31.7, 34.7, 35.7, 36.9, 38.0, 44.9, 47.7, 49.6, 54.5, 55.5, 71.1, 110.8, 120.2, 124.7, 127.7, 129.6, 130.7, 136.0, 158.7 and 209.8.

*2.1.3. (E)-16-(3-Bromophenyl)methylidene-trans-androsterone (**2h**)*

Obtained as white solid; Yield 96%; m.p. 176–178 °C; ^{1}H NMR 0.72–0.78 (m, 1H), 0.87 (s, 3H), 0.95 (s, 3H), 0.95–1.03 (m, 1H), 1.15–1.43 (m, 7H), 1.57–1.95 (m, 9H), 2.35–2.46 (m, 1H), 2.83 (dd, *J* = 15.9, 6.3 Hz, 1H), 3.57–3.64 (m, 1H), 4.78 (brs, 1H), 7.25–7.33 (m, 2H), 7.43–7.49 (m, 2H), 7.65 (s, 1H). ^{13}C NMR 12.3, 14.5, 20.5, 28.4, 29.1, 31.1, 31.4, 31.6, 34.7, 35.7, 36.9, 38.0, 44.8, 47.7, 49.4, 54.5, 71.1, 122.8, 128.8, 130.2, 131.3, 132.0, 132.7, 137.5, 137.7 and 209.5.

*2.1.4. (E)-16-(Naphthyl)methylidene-trans-androsterone (**2k**)*

Obtained as white solid; Yield 96%; m.p. 172–174 °C; ^{1}H NMR 0.65–0.76 (m, 1H), 0.86 (s, 3H), 0.92–0.99 (m, 2H), 1.02 (s, 3H), 1.06–1.48 (m, 7H), 1.55–1.99 (m, 8H), 2.38–2.49 (m, 1H), 2.72 (dd, *J* = 15.9, 6.3 Hz, 1H), 3.52–3.61 (m, 1H), 5.09 (brs, 1H), 7.47–7.63 (m, 4H), 7.85–7.89 (m, 2H), 8.13–8.17 (m, 1H), 8.19 (s, 1H). ^{13}C NMR 12.3, 14.5, 20.6, 28.4, 29.4, 31.1, 31.4, 31.8, 34.7, 35.7, 36.9, 38.0, 44.8, 48.1, 49.5, 54.5, 71.1, 124.1, 125.1, 126.2, 126.6, 126.9, 128.7, 129.6, 129.9, 132.2, 132.5, 133.6, 138.4 and 209.5.

*2.1.5. (E)-16-(4-Bromophenyl)methylidene-trans-dehydroandrosterone (**5c**)*

Obtained as white solid; Yield 96%; m.p. 254–256 °C; ^{1}H NMR 0.98 (s, 3H), 1.08 (s, 3H), 1.04–1.15 (m, 2H), 1.24–1.67 (m, 6H), 1.72–2.00 (m, 5H), 2.17–2.46 (m, 4H), 2.84 (dd, *J* = 15.8, 6.5 Hz, 1H), 3.50–3.59 (m, 1H), 5.39–5.41 (m, 1H), 7.36–7.41 (m, 3H), 7.53–7.56 (m, 2H). ^{13}C NMR 14.2, 19.4, 20.4, 29.3, 31.0, 31.2, 31.6, 31.7, 36.7, 37.2, 42.2, 47.3, 49.8, 50.4, 71.6, 120.7, 123.4, 131.6, 131.7, 131.9, 134.6, 136.7, 141.2 and 209.6.

*2.1.6. (E)-16-(4-Fluorophenyl)methylidene-trans-dehydroandrosterone (**5d**)*

Obtained as white solid; Yield 98%; m.p. 248–250 °C; ^{1}H NMR 0.98 (s, 3H), 1.10 (s, 3H), 1.02–1.16 (m, 2H), 1.31–1.66 (m, 4H), 1.71–2.01 (m, 7H), 2.17–2.47 (m, 4H), 2.85 (dd, *J* = 15.7, 5.3 Hz, 1H), 3.50–3.59 (m, 1H), 5.3–3.41 (m, 1H), 7.08–7.13 (m, 2H), 7.40 (s, 1H), 7.51–7.55 (m, 2H). ^{13}C NMR 14.2, 19.5, 20.4, 29.2, 30.9, 31.2, 31.5, 31.6, 36.7, 37.1, 42.2, 47.3, 49.9, 50.3, 71.6, 115.7, 116.0, 120.8, 131.9, 132.1, 132.2, 135.5, 135.6, 141.2, 161.4, 164.7 and 209.5.

*2.1.7. (E)-16-(4-Methylphenyl)methylidene-trans-dehydroandrosterone (**5e**)*

Obtained as white solid; Yield 97%; m.p. 272–274 °C; ^{1}H NMR 0.98 (s, 3H), 1.01–1.14 (m, 2H), 1.07 (s, 3H), 1.31–1.66 (m, 4H), 1.71–2.00 (m, 7H), 2.17–2.48 (m, 3H), 2.38 (s, 3H), 2.88 (dd, *J* = 15.8, 6.1 Hz, 1H), 3.52–3.55 (m, 1H), 4.82 (brs, 1H), 5.39–5.41 (m, 1H), 7.21–7.27 (m, 2H), 7.43–7.46 (m, 3H). ^{13}C NMR 14.3, 19.5, 20.4, 21.5, 29.4, 30.9, 31.2, 31.6, 36.7, 37.1, 42.2, 47.3, 49.9, 50.4, 71.6, 120.8, 129.5, 130.4, 132.8, 133.2, 135.0, 139.6, 141.2 and 209.9.

*2.1.8. (E)-16-(2-Chlorophenyl)methylidene-trans-dehydroandrosterone (**5g**)*

Obtained as white solid; Yield 97%; m.p. 250–252 °C; ^{1}H NMR 1.00 (s, 3H), 1.07 (s, 3H), 1.06–1.15 (m, 2H), 1.29–1.65 (m, 5H), 1.70–1.90 (m, 5H), 1.97–2.21 (m, 2H), 2.26–2.48 (m, 3H), 2.75 (dd, *J* = 15.9, 6.3 Hz, 1H), 3.49–3.58 (m, 1H), 5.37–5.38 (m, 1H), 7.27–7.33 (m, 2H), 7.41–7.55 (m, 2H), 7.78 (s, 1H). ^{13}C NMR 14.2, 19.5, 20.4, 29.2, 30.9, 31.2, 31.6, 36.7, 37.1, 49.2, 47.5, 49.8, 50.3, 71.6, 120.8, 126.6, 129.2, 129.9, 130.0, 133.8, 135.7, 138.2, 141.2 and 208.9.

*2.1.9. (E)-16-(2-Methylphenyl)methylidene-trans-dehydroandrosterone (**5h**)*

Obtained as white solid; Yield 98%; m.p. 215–217 °C; ^{1}H NMR 1.00 (s, 3H), 1.07 (s, 3H), 1.06–1.14 (m, 2H), 1.26–1.89 (m, 10H), 1.97–2.17 (m, 2H), 2.26–2.36 (m, 3H), 2.41 (s, 3H), 2.76 (dd, *J* = 16.1, 5.9 Hz, 1H), 3.52–3.56 (m, 1H), 5.37–5.38 (m, 1H), 7.24–7.25 (m, 3H), 7.46–7.47 (m, 1H), 7.67 (s, 1H). ^{13}C NMR 14.2, 19.5, 19.9, 20.4, 29.3, 30.9, 31.2, 31.6, 36.7, 37.2, 42.2, 47.6, 50.0, 50.4, 71.6, 120.8, 125.8, 126.4, 128.6, 129.0, 130.6, 130.8, 134.4, 136.6, 138.7, 141.2 and 209.4.

*2.1.10. (E)-16-(2-Methoxyphenyl)methylidene-trans-dehydroandrosterone (**5i**)*

Obtained as white solid; Yield 96%; m.p. 128–130 °C; ^{1}H NMR 0.99 (s, 3H), 1.07 (s, 3H), 1.08–1.14 (m, 2H), 1.28–1.90 (m, 10H), 1.96–2.20 (m, 2H), 2.26–2.48 (m, 3H), 2.80 (dd, *J* = 15.6, 6.3 Hz, 1H), 3.50–3.57 (m, 1H), 3.86 (s, 3H), 5.37–5.39 (m, 1H), 6.90–7.01 (m, 2H), 7.32–7.51 (m, 2H), 7.86 (s, 1H). ^{13}C NMR 14.2, 19.5, 20.4, 29.4, 30.9, 31.2, 31.6, 36.7, 37.1, 42.2, 47.4, 50.0, 50.3, 55.5, 71.6, 110.8, 120.2, 120.9, 124.7, 127.9, 129.6, 130.7, 135.9, 141.1, 158.7 and 209.6.

*2.1.11. (E)-16-(3-Bromophenyl)methylidene-trans-dehydroandrosterone (**5j**)*

Obtained as white solid; Yield 97%; m.p. 222–224 °C; ^{1}H NMR 0.98 (s, 3H), 1.08 (s, 3H), 1.02–1.15 (m, 2H), 1.31–1.67 (m, 8H), 1.72–2.01 (m, 3H), 2.18–2.50 (m, 4H), 2.86 (dd, *J* = 16.2, 6.3 Hz,