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Synthesis of novel 16-spiro steroids: 7-(Aryl)tetrahydro-1*H*-pyrrolo [1,2-*c*][1,3]thiazolo estrone hybrid heterocycles

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ABSTRACT

The 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the reaction of isatins or acenaphthylene-1,2-dione and 1,3-thiazolane-4-carboxylic acid to various exocyclic dipolarophiles synthesized from estrone afforded a library of novel C-16 spiro oxindole or acenaphthylene-1-one – 7-(aryl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole – estrone hybrid heterocycles. These reactions occur regio- and stereo-selectively affording a single isomer of the spiro estrones in excellent yields with the formation of two C–C and one C–N bonds along with the generation of four new contiguous stereo-centers in a single step.

1. Introduction

Steroids form a group of structurally related compounds widely distributed in nature and posses a broad spectrum of biological activities. Synthetic derivatives of steroids have also attracted a good deal of attention for the purpose of developing lead compounds to treat several diseases. In particular, the syntheses of steroids comprising heterocycles have received much attention of the chemists since many of such compounds have been shown to display important pharmacological properties [1].

Spiro steroids are ubiquitous in nature, for instance spirostanes, which include a spiro-acetal moiety in the structure have been shown to posses significant biological properties [2]. Further, it is noteworthy that investigations pertaining to the synthesis of steroids comprising a spiro heterocycle at C-17 [3] have gained much importance whereas the reports on the synthesis of C-16 spiro heterocyclic steroids are scarce [4]. The known C-16 spiro steroids are the cycloalkano derivatives [5], dioxaphosphorinanes [6], pyrazolines [7] and pyrrolidines [8]. In general, 1,3-dipolar cycloadditions offer a facile route towards the construction of spiro heterocycles and in particular, the cycloaddition of azomethine ylides to exocyclic olefins are among the best employed protocol for the construction of spiro-pyrrolidines, pyrrolizines, pyrrolothiazoles and octahydroindolizines [9]. Recently, we reported the synthesis of novel C-16 spiro steroids comprising *trans*-androsterone/dehydroandrosterone–tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole hybrid heterocycles [10] via 1,3-dipolar cycloaddition. In view of our continuous interest in synthesizing hybrid C-16 spiro steroids, we herein report for the first time the synthesis of novel C-16 spiro pyrrolo[1,2-*c*][1,3]thiazole containing estrone hybrid heterocycles.

Incidentally, estrone is a very vital steroid that has key role in many biological processes. Numerous methods for the synthesis of modified estrone derivatives have been reported in view of their wide range of biological applications. For instance, estrone derivatives are used as potent inhibitors of 17β-hydroxysteroid dehydrogenase type1 [11], steroid sulfatase inhibitors [12] and also exhibits antiproliferative [13], anticancer [14], antimicrobial and antifungal activities [15]. Many of the drugs for menopausal estrogen therapy contain estrone core [16].

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 II Elemental CHNS analyzer. The single crystal X-ray data of **2b** were collected on Enraf–Nonius (CAD4) diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation. Scan range was $2.02° \leqslant \theta \leqslant 24.97°$. 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.

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All the chemicals were purchased from Aldrich and used without any further purification.

2.1. General procedure for the synthesis of 16-(E)-arylidene-estrones **2**

A mixture of estrone **1** (1 mmol) and aromatic aldehyde (1 mmol) were dissolved in ethanol (5 mL) to which an alcoholic solution of potassium hydroxide (20%) was added. The mixture was refluxed on an oil bath with continuous stirring for 5 h and the progress of the reaction was monitored by TLC intermittently. After completion of the reaction, the mixture was allowed to cool. The precipitated solid was filtered, washed with water (100 mL) and dried under vacuum to afford the product **2** as yellow solid. The yields of the 16-(*E*)-arylidene-estrones **2** were almost quantitative except for the loss during work-up.

2.2. General procedure for the synthesis of spiro[5′.3″]oxindole/acenaphthylene-1″-one-spiro[6′.16]-7′-(aryl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrones **3**–**5**

A mixture of **2** (1 mmol), isatin/5-chloro-isatin/acenaphthylene-1,2-dione (1.1 mmol) and 1,3-thiazolane-4-carboxylic acid (1.2 mmol) were taken in isopropanol (10 mL) and boiled to reflux for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction as evident from TLC, the reaction mixture was poured into ice water (50 mL). The resultant precipitate was filtered, dried and purified by flash filtration column on silica gel employing petroleum ether/ethyl acetate (90:10) as eluting solvent to get the products **3**, **4** or **5**.

2.2.1. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(phenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3a**)

Isolated as pure white solid; yield 82%; mp 185–186 °C; Anal. Calcd. for $C_{36}H_{36}N_2O_3S$: C, 74.97; H, 6.29; N, 4.86. Found: C, 74.89; H, 6.38; N, 4.80. ^{1}H NMR 0.32 (s, 3H), 0.50–0.60 (m, 1H), 0.95–0.97 (m, 1H), 1.04–1.18 (m, 2H), 1.23–1.33 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.68 (m, 2H), 1.80–1.84 (m, 1H), 2.01–2.05 (m, 1H), 2.50–2.51 (m, 1H), 2.54–2.69 (m, 2H), 2.82–2.95 (m, 2H), 3.63 (d, *J* = 6.6 Hz, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 4.74–4.81 (m, 2H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.04–7.34 (m, 7H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H). ^{13}C NMR 14.3, 25.2, 26.5, 29.0, 31.3, 31.4, 33.5, 36.9, 44.0, 47.2, 48.4, 55.1, 72.2, 72.7, 74.6, 109.7, 112.7, 115.3, 115.6, 122.3, 125.7, 126.0, 127.5, 128.5, 129.5, 129.8, 131.6, 137.1, 137.7, 140.6, 153.4, 179.1 and 219.5.

2.2.2. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-chlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3b**)

Isolated as white solid; yield 84%; mp 200–201 °C; Anal. Calcd. for $C_{36}H_{35}ClN_2O_3S$: C, 70.74; H, 5.77; N, 4.58. Found: C, 70.71; H, 5.73; N, 4.54. ^{1}H NMR 0.39 (s, 3H), 0.49–0.56 (m, 1H), 0.73–0.75 (m, 1H), 0.98–1.06 (m, 2H), 1.15–1.20 (m, 2H), 1.26–1.42 (m, 1H), 1.60–1.67 (m, 2H), 1.79–1.82 (m, 1H), 2.02–2.06 (m, 1H), 2.43 (d, *J* = 9.3 Hz, 1H), 2.71 (m, 2H), 2.79–2.91 (m, 2H), 3.59 (dd, *J* = 12.9, 6.0 Hz, 2H), 4.68–4.74 (m, 2H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 9.6 Hz, 1H) 7.06 (t, *J* = 7.5 Hz, 1H), 7.21–7.39 (m, 6H), 7.57 (s, 1H). ^{13}C NMR 14.7, 25.3, 26.6, 29.1, 31.2, 33.1, 36.9, 44.1, 47.1, 47.2, 54.3, 72.2, 72.7, 74.3, 109.6, 112.8, 115.3, 122.6, 125.8, 126.1, 128.9, 129.4, 129.9, 131.3, 133.4, 136.1, 137.7, 140.7, 153.5, 178.5 and 219.7.

2.2.3. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-fluorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3c**)

Isolated as white solid; yield 81%; mp 190–191 °C; Anal. Calcd. for $C_{36}H_{35}FN_2O_3S$: C, 72.70; H, 5.93; N, 4.71. Found: C, 72.67; H, 5.90; N, 4.68. ^{1}H NMR 0.33 (s, 3H), 0.49–0.59 (m, 1H), 0.95–1.05 (m, 1H), 1.10–1.20 (m, 2H), 1.23–1.28 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.66 (m, 2H), 1.80–1.82 (m, 1H), 2.00–2.04 (m, 1H), 2.48–2.51 (m, 1H), 2.64–2.67 (m, 2H), 2.80–2.93 (m, 2H), 3.61 (m, 2H), 3.70 (d, *J* = 9.6 Hz, 1H), 4.71 (dt, *J* = 7.6, 6.6 Hz, 1H), 5.06 (s, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.00–7.25 (m, 6H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.85 (s, 1H). ^{13}C NMR 14.6, 26.4, 28.8, 31.1, 31.3, 33.2, 34.4, 36.7, 40.3, 43.8, 47.2, 54.2, 72.1, 72.5, 74.3, 109.6, 112.6, 115.2, 115.5, 121.3, 122.3, 125.5, 125.8, 129.3, 129.7, 131.4, 132.8, 136.4, 137.5, 140.5, 153.3, 178.9 and 219.4.

2.2.4. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-bromophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3d**)

Isolated as white solid; yield 80%; mp 290–291 °C; Anal. Calcd. for $C_{36}H_{35}BrN_2O_3S$: C, 65.95; H, 5.38; N, 4.27. Found: C, 65.87; H, 5.49; N, 4.12. ^{1}H NMR 0.39 (s, 3H), 0.48–0.57 (m, 1H), 0.96–1.01 (m, 1H), 1.08–1.15 (m, 2H), 1.21–1.29 (m, 1H), 1.60–1.61 (m, 2H), 1.63–1.67 (m, 2H), 1.80–1.83 (m, 1H), 2.00–2.04 (m, 1H), 2.41–2.48 (m, 1H), 2.55–2.73 (m, 2H), 2.82–2.87 (m, 2H), 3.56 (d, *J* = 6.0 Hz, 1H), 3.61 (d, *J* = 6 Hz, 1H), 3.67 (m, 1H), 4.72 (dt, *J* = 7.6, 6.6, 1H), 4.96 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.03–7.26 (m, 5H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 1H). ^{13}C NMR 14.7, 25.2, 26.5, 28.9, 31.1, 31.3, 33.0, 34.3, 36.8, 44.0, 47.1, 54.3, 72.1, 72.6, 74.5 109.5, 112.7, 115.2, 115.4, 121.5, 122.6, 125.8, 126.0, 129.3, 129.8, 131.5, 131.8, 136.6, 137.7, 140.7, 153.4, 178.3 and 219.7.

2.2.5. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-methylphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3e**)

Isolated as white solid; yield 85%; mp 199–200 °C; Anal. Calcd. for $C_{37}H_{38}N_2O_3S$: C, 75.22; H, 6.48; N, 4.74. Found: C, 75.34; H, 6.57; N, 4.79. ^{1}H NMR 0.33 (s, 3H), 0.52–0.59 (m, 1H), 0.95–0.97 (m, 1H), 1.00–1.18 (m, 2H), 1.23–1.33 (m, 1H), 1.59–1.74 (m, 4H), 1.81–1.84 (m, 1H), 1.99–2.04 (m, 1H), 2.33 (s, 3H), 2.51–2.56 (m, 1H), 2.64–2.67 (m, 2H), 2.80–2.95 (m, 2H), 3.61 (d, *J* = 6.6 Hz, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 3.70 (d, *J* = 9.6 Hz, 1H), 4.74 (dt, *J* = 6.6, 9.3 Hz, 1H), 5.03 (s, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.1, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.03–7.26 (m, 7H), 7.80 (s, 1H). ^{13}C NMR 14.3, 25.3, 26.5, 30.0, 31.3, 31.5, 33.7, 34.6, 44.0, 47.3, 47.4, 54.3, 55.0, 72.4, 72.8, 74.6, 109.8, 112.7, 113.4, 115.4, 122.3, 125.7, 126.0, 129.3, 129.5, 129.8, 131.6, 133.8, 137.2, 137.6, 140.6, 153.4, 179.5 and 220.0.

2.2.6. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-methoxyphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3f**)

Isolated as white solid; yield 86%; mp 214–215 °C; Anal. Calcd. for $C_{37}H_{38}N_2O_4S$: C, 73.24; H, 6.31; N, 4.62. Found: C, 73.12; H, 6.23; N, 4.69. ^{1}H NMR 0.29 (s, 3H), 0.52–0.60 (m, 1H), 0.95–1.00 (m, 1H), 1.03–1.18 (m, 2H), 1.23–1.30 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.70 (m, 2H), 1.80–1.83 (m, 1H), 1.99–2.04 (m, 1H), 2.52–2.57 (m, 1H), 2.63–2.65 (m, 2H), 2.80–2.96 (m, 2H), 3.61 (d, *J* = 6.9 Hz, 1H), 3.65 (d, *J* = 6.9, 1H), 3.69 (d, *J* = 9.6 Hz, 1H), 3.78 (s, 3H), 4.71 (dt, *J* = 6.0, 9.9 Hz, 1H), 5.34 (s, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.03–7.25 (m, 6H), 7.50 (d, *J* = 7.8 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR 14.2, 25.0, 26.3, 28.8, 30.9, 31.2, 32.7, 36.6, 43.7, 46.5, 47.0, 54.7, 71.8, 72.5, 72.9, 73.7, 109.3, 112.5, 113.5, 115.0, 121.3, 125.4, 125.4, 128.4, 129.2, 130.0, 130.5, 134.0, 137.0, 141.8, 154.5, 158.4, 178.1 and 219.7.