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Efficient three-component one-pot synthesis of steroidal polysubstituted anilines

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ABSTRACT

An efficient and practical base-promoted cascade reaction has been developed to access steroidal polysubstituted anilines from simple precursors. The protocol reported herein achieved the formation of a benzene ring as well as three continuous C–C bonds in a single operation. The reaction mechanism was proposed on the basis of the key intermediate obtained. Besides, this method could be potentially employed for the synthesis of biphenyl compounds. The adjacent amine and nitrile groups existed in the final products have the potential for late stage functionalization, which would provide efficient access to steroidal compound collections with structural diversity and complexity.

1. Introduction

Steroids are an important class of multi-cyclic compounds that exhibit diverse biological activities in living organisms. These biologically important properties of modified steroids depend on structural features of the steroid ring system [1] and side chain [2]. Therefore, modifications on the steroid ring system and side chain, especially the introduction of heterocycles, have drawn wide attention in steroid chemistry, numerous structure activity relationships have been established by such synthetic alterations [3]. Representative examples are abiraterone [4–7] and galeterone [8] (Fig. 1), which have been used in clinic for the treatment of advanced prostate cancers. Very recently, our group incorporated biologically promising spirooxindole scaffolds into the steroid core [9,10], generating a library of steroidal spirooxindoles with good anticancer activity (IC_{50} < 10 μM) (Fig. 1) [11,12].

By contrast, reports about the introduction of benzene ring into the steroid scaffold have been relatively rare. It seems that such ring system has escaped from our attention in drug discovery programs. In fact, benzene scaffolds with suitable substituents have been reported to possess diverse biological properties and can also serve as important synthetic intermediates [13–16]. Additionally, polysubstituted biphenyl derivatives are also found in numerous natural products and pharmaceutical agents [17–22]. Therefore, the introduction of benzene scaffolds into the steroid nucleus is needed and would open a new avenue for designing novel steroids with new or improved properties.

In continuation of our previous work in developing new biologically active modified steroids [11,12,23–28], we herein report a base-promoted three-component one-pot method for the synthesis of steroidal polysubstituted anilines from steroidal α,α-dicyanoalkene, aromatic aldehydes and malononitrile. To the best of our knowledge, this is the first report about the synthesis of steroidal polysubstituted anilines.

2. Experimental

2.1. General remarks

All reagents and solvents used were of analytical grade purchased from commercial sources without special treatment. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel. Melting points were determined on a Beijing Keyi XT4A apparatus and are uncorrected. All NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer with TMS as internal standard in DMSO-*d*6 or $CDCl_3$. Chemical shifts are given as δ ppm values relative to TMS (Most of the peaks due to the steroidal skeleton are merged and could not be differentiated. Thus δ values of only those peaks that distinguish the product and could easily be

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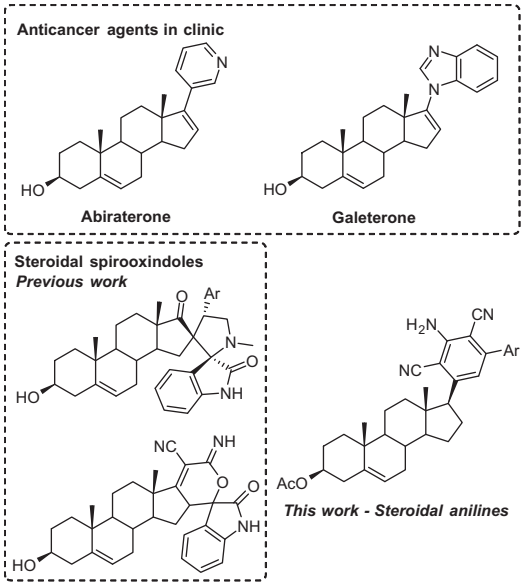

Fig. 1. Steroidal heterocycles with anticancer activity previously reported and the target molecules synthesized in this work.

differentiated are reported). High-resolution mass spectra (HRMS) were recorded on Esquire3000 mass spectrometer by atmospheric-pressure chemical ionization (APCI).

*2.2. General procedure for the synthesis of steroidal polysubstituted anilines **4a-j***

Compound **1** was synthesized from pregnenolone following our previously reported method [29]. To a solution of compound **1** (1.0 mmol) in ethanol (99.7%), aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol) and piperidine (1.5 mmol) were added sequentially. The reaction mixture was stirred at room temperature for the time indicated in Scheme 1. After removal of the solvent, the residue was purified by column chromatography with ethyl acetate/petroleum ether (1/9) as the eluent to give the corresponding steroidal polysubstituted anilines (Scheme 1).

*2.2.1. 2,6-Dicyano-3-(4″-chlorophenyl)-5-[(3′β,17′β)-3′-(acetyloxy)androst-5′-en-17′-yl]aniline (**4a**)*

White solid, yield 83%, m.p. 197.3–199.0 °C. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 6.81 (s, 1H), 6.65 (s, 2H), 5.37 (d, *J* = 5.1 Hz, 1H), 4.54–4.39 (m, 1H), 3.09 (t, *J* = 9.5 Hz, 1H), 1.99 (s, 3H), 0.96 (s, 3H), 0.58 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 170.2, 153.9, 151.7, 147.8, 140.0, 137.1, 134.6, 130.9, 129.1, 122.4, 117.7, 116.7, 116.5, 97.6, 93.4, 73.6, 56.6, 55.3, 49.9, 46.7, 38.1, 37.6, 36.9, 36.6, 32.3, 31.7, 27.8, 27.2, 24.8, 21.5, 20.7, 19.4, 13.4. HRMS (APCI): *m*/*z* calcd for $C_{35}H_{39}ClN_3O_2$ $(M+H)^+$, 568.2731; found, 568.2722.

*2.2.2. 2,6-Dicyano-3-(1″-naphthyl)-5-[(3′β,17′β)-3′-(acetyloxy)androst-5′-en-17′-yl]aniline (**4b**)*

White solid, yield 75%, m.p. 297.1–298.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.98 (t, *J* = 8.2 Hz, 2H), 7.64–7.43 (m, 5H), 6.88 (s, 1H), 5.41 (d, *J* = 5.0 Hz, 1H), 5.28 (s, 2H), 4.71–4.59 (m, 1H), 3.28 (t, *J* = 9.5, 1H), 2.06 (s, 3H), 1.06 (s, 1.8H), 1.03 (s, 1.2H), 0.68 (s, 1.8H), 0.60 (s, 1.2H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) δ 170.5, 152.3, 151.0, 148.0, 147.9, 139.8, 135.5, 133.7, 133.7, 130.9, 129.7, 129.7, 128.7, 128.6, 127.0, 126.9, 126.8, 126.4, 126.3, 125.2, 124.9, 124.9, 122.3, 120.5, 116.4, 115.5, 98.0, 96.4, 73.8, 56.5, 55.5, 55.4, 49.9, 47.4, 47.0, 38.1, 37.7, 37.5, 37.0, 36.7, 32.3, 31.9, 29.7, 29.4, 27.7, 27.4, 24.8, 21.4, 20.8, 20.7, 19.4, 13.4, 13.2. HRMS (APCI): *m*/*z* calcd for $C_{39}H_{42}N_3O_2$ $(M+H)^+$, 584.3277; found, 584.3277.

*2.2.3. 2,6-Dicyano-3-(4″-fluorophenyl)-5-[(3′β,17′β)-3′-(acetyloxy)androst-5′-en-17′-yl]aniline (**4c**)*

White solid, yield 80%, m.p. 228.4–229.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.8, 5.1 Hz, 2H), 7.21 (t, *J* = 8.7 Hz, 2H), 6.78 (s, 1H), 5.42 (d, *J* = 5.4 Hz, 1H), 5.26 (s, 2H), 4.68–4.60 (m, 1H), 3.22 (t, *J* = 9.5 Hz, 1H), 2.06 (s, 3H), 1.04 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.6, 151.5, 147.7, 139.8, 130.4, 130.3, 122.2, 118.7, 116.3, 116.1, 116.0, 115.9, 97.9, 94.0, 73.8, 56.5, 55.5, 49.9, 47.0, 38.1, 37.4, 37.0, 36.7, 32.3, 31.8, 27.7, 27.5, 24.8, 21.4, 20.7, 19.3, 13.3. HRMS (APCI): *m*/*z* calcd for $C_{35}H_{39}FN_3O_2$ $(M+H)^+$, 552.3026; found, 552.3023.

*2.2.4. 2,6-Dicyano-3-(4″-pyridyl)-5-[(3′β,17′β)-3′-(acetyloxy)androst-5′-en-17′-yl]aniline (**4d**)*

White solid, yield 85%, m.p. 265.7–267.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 5.4 Hz, 2H), 7.45 (d, *J* = 5.4 Hz, 2H), 6.79 (s, 1H), 5.41 (d, *J* = 5.8 Hz, 1H), 5.38 (s, 2H), 4.68–4.58 (m, 1H), 3.24 (t, *J* = 9.5 Hz, 1H), 2.05 (s, 3H), 1.03 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.7, 152.2, 150.4, 145.6, 145.4, 139.8, 122.8, 122.2, 118.3, 115.9, 115.4, 99.1, 93.5, 73.8, 56.5, 55.6, 49.8, 47.1, 38.1, 37.4, 37.0, 36.7, 32.3, 31.8, 27.7, 27.6, 24.8, 21.4, 20.7, 19.3, 13.3. HRMS (APCI): *m*/*z* calcd for $C_{34}H_{39}N_4O_2$ $(M+H)^+$, 535.3073; found, 535.3070.

*2.2.5. 2,6-Dicyano-3-(4″-methylphenyl)-5-[(3′β,17′β)-3′-(acetyloxy)androst-5′-en-17′-yl]aniline (**4e**)*

White solid, yield 79%, m.p. 140.0–141.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.81 (s, 1H), 5.42(d, *J* = 5.4 Hz, 1H), 5.24 (s, 2H), 4.69–4.58 (m, 1H), 3.22 (t, *J* = 9.6 Hz, 1H), 2.45 (s, 3H), 2.06 (s, 3H), 1.04 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.6, 151.2, 148.9, 139.8, 139.7, 135.0, 129.6, 128.3, 122.3, 118.8, 116.5, 116.2, 97.5, 94.0, 73.8, 56.5, 55.5, 49.9, 46.9, 38.1, 37.4, 37.0, 36.7, 32.3, 31.8, 27.7, 27.5, 24.8, 21.4, 21.4, 20.7, 19.3, 13.2. HRMS (APCI): *m*/*z* calcd for $C_{36}H_{42}N_3O_2$ $(M+H)^+$, 548.3277; found, 548.3270.

*2.2.6. 2,6-Dicyano-3-(4″-methoxylphenyl)-5-[(3′β,17′β)-3′-(acetyloxy)androst-5′-en-17′-yl]aniline (**4f**)*

White solid, yield 79%, m.p. 168.5–169.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.79 (s, 1H), 5.42 (d, *J* = 5.6 Hz, 1H), 5.23 (s, 2H), 4.72–4.53 (m, 1H), 3.89 (s, 3H), 3.21 (t, *J* = 9.5 Hz, 1H), 2.06 (s, 3H), 1.04 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 160.7, 152.7, 151.1, 148.5, 139.8, 130.2, 129.8, 122.3, 118.6, 116.5, 116.4, 114.3, 97.2, 93.8, 73.8, 56.5, 55.5, 55.4, 49.9, 46.9, 38.1, 37.4, 37.0, 36.7, 32.3, 31.8, 27.7, 27.5, 24.8, 21.4, 20.7, 19.3, 13.2. HRMS (APCI): *m*/*z* calcd for $C_{36}H_{42}N_3O_3$ $(M+H)^+$, 564.3226; found, 564.3229.

*2.2.7. 2,6-Dicyano-3-(2″-furyl)-5-[(3′β,17′β)-3′-(acetyloxy)androst-5′-en-17′-yl]aniline (**4g**)*

White solid, yield 77%, m.p. >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.40 (s, 1H), 7.22 (s, 1H), 6.60 (s, 1H), 5.40 (d, *J* = 4.6 Hz, 1H), 5.30 (s, 2H), 4.74–4.51 (m, 1H), 3.17 (t, *J* = 9.5 Hz, 1H), 2.05 (s, 3H), 1.02 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 153.0, 151.4, 149.3, 144.3, 139.8, 135.5, 122.3, 116.5, 116.5, 114.3, 112.6, 112.6, 97.0, 89.0, 73.8, 56.5, 55.5, 49.9, 46.9, 38.1, 37.5, 37.0, 36.7, 32.3, 31.8, 27.7, 27.4, 24.8, 21.4, 20.7, 19.3, 13.2. HRMS (APCI): *m*/*z* calcd for $C_{33}H_{38}N_3O_3$ $(M+H)^+$, 524.2913; found, 524.2909.