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Microwave promoted one-pot synthesis of novel A-ring fused steroidal dehydropiperazines

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ABSTRACT

The preparation of ring-A fused steroidal dehydropiperazine at the 3,4-position is herein described. The novel steroidal dehydropiperazines were prepared from the annulation reaction of ethylenediamine with 3-keto-4-en steroids in a one-pot reaction under microwave irradiation. The key step involves base catalysed aerial oxidation of the C-6 methylene group followed by cyclocondensation of ethylenediamine via Michael addition reaction.

1. Introduction

A-ring hetero steroids have attracted great attention because of their pharmaceutical properties [1]. Continued efforts are being made to annelate steroidal moiety with pyrazole, isoxazole, pyridine, pyrrolo or pyrimidine rings as many of these heterosteroids possess potent biological activities [2–14]. The pyrazine fused bissteroid cephalostatin has shown powerful cell growth inhibition against P388 lymphocytic leukemia [15,16]. On the contrary, the piperazine constitutes an important class of heterocycles owing to wide spectrum of biological activities [17,18]. Christiansen and Clinton have described the preparation of biologically active steroidal piperazine fused to 2,3-position of steroidal nucleus [19]. These were prepared in two steps – (a) condensation of androst-2,3-dione with ethylenediamine to steroidal pyrazine, and (b) hydrogenation of steroidal pyrazine to steroidal piperazine. However, there is a lack of attention for the development of synthetic strategy for A-ring fused piperazines at 3,4-position of steroidal moiety.

In view of the therapeutic importance of A-ring heterosteroids as well as piperazines, we were interested to prepare piperazine fused steroids from readily available A-ring conjugated ketosteroids. Herein, we wish to report a microwave promoted convenient preparation of steroidal dehydropiperazine from the one-pot reaction of 3-keto-4-en steroids with ethylenediamine.

2. Experimental

2.1. General Remarks

All reactions were performed as per standard procedure using Aldrich aluminium oxide active basic (Brockmann grade I, ~150 mesh) and monitored on Merck aluminium thin layer chromatography (TLC, $UV_{254\,nm}$) plates. Column chromatography was carried out on silica gel (60–120 mesh, Merck chemicals). Melting points were determined in open capil-

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lary tubes on Buchi B-540 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer using KBr pellets or on a thin film using chloroform. All the ^{1}H and ^{13}C NMR spectra were recorded on Brucker Avance DPX 300 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shift values were given as δ ppm values. ESI mass spectra were recorded on a Brucker Daltonic Data Analysis 2.0 spectrometer. Elemental analysis was performed on Perkin Elmer Series II CSNS/O Model 2400 machine calibrated against standard acetanilide.

2.2. Organic synthesis

Steroid (1.04 mmol) and ethylenediamine (5.2 mmol) were intimately mixed with basic alumina (1.0 g) in a mortar and irradiated in an open reaction vessel of a Synthwave 402 Prolabo focused microwave reactor for 5–8 min after setting reaction temperature at 120 °C and power at 60% (maximum output 300 W). On completion of reaction (vide TLC), the reaction mixture was treated with water (50 ml), extracted with dichloromethane (3 × 30 ml). The organic portion was washed with water, dried over anhydrous sodium sulfate and the solvent removed to obtain a crude product. Silica gel column chromatography separation using EtOAc/hexane (4:6) as eluant over silica gel afforded the purified product.

2.2.1. 4′-Dehydro-cholest-4-eno[3,4-e]piperazin-6-one 2a

Brown crystals, yield 90%; mp: 128–130 °C; IR cm^{-1}: 3490, 2952, 1630, 1582, 1544, 1467, 1280; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.07 (bs, 1H, —NH), 3.75 (m, 2H, =N—CH_2—), 3.22 (m, 2H, —NH—CH_2—), 1.10 (s, 3H, 19—CH_3), 0.71 (s, 3H, 18—CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 200.7, 163.5, 141.7, 113.5, 57.3, 56.3, 50.0, 47.0, 44.4, 42.7, 39.9, 36.7, 36.5, 36.1, 35.0, 32.4, 28.6, 28.4 (2C), 24.3, 24.2, 23.2, 23.0 (2C), 22.4, 21.7, 21.6, 19.1, 12.3. ESI mass m/z = 439 [M^+ + 1]. Anal calcd. for $C_{29}H_{46}N_2O$: C, 79.40; H, 10.57; N, 6.38. Found: C, 79.66; H, 10.31; N, 6.20.

2.2.2. 17β-Hydroxy-4′-dehydro-androst-4-eno[3,4-e]piperazin-6-one 2b

Gum, yield 88%; IR cm^{-1}: 3376, 2940, 1671, 1582, 1541, 1454, 1277; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.10 (bs, 1H, —NH), 3.61 (m, 2H, =N—CH_2—), 3.18 (m, 2H, —NH—CH_2—), 1.12 (s, 3H, 19—CH_3), 0.75 (s, 3H, 18—CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 200.7, 163.4, 142.3, 113.4, 82.0, 51.3, 51.0, 50.5, 47.8, 44.3, 43.6, 39.5, 37.2, 36.4, 35.5, 32.9, 31.0, 23.9, 22.9, 21.8, 12.0. ESI mass m/z = 343 [M^+ + 1].

2.2.3. 17β-Acetoxy-4′-dehydro-androst-4-eno[3,4-e]piperazin-6-one 2c

Gum, yield 85%; IR cm^{-1}: 3375, 2925, 1732, 1663, 1583, 1541, 1465, 12775; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.05 (bs, 1H, —NH), 4,45 (t, 1H, J = 8.2 Hz, 17—CH—), 3.60 (m, 2H, =N—CH_2—), 3.21 (m, 2H, —NH—CH_2—), 1.12 (s, 3H, 19—CH_3), 1.05 (s, 3H, 17—$OCOCH_3$), 0.76 (s, 3H, 18—CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 170.8, 162.6, 143.5, 114.1, 87.3, 82.5, 51.9, 51.2, 50.9, 48.0, 44.5, 43.8, 39.2, 38.2, 37.0, 36.1, 33.5, 31.7, 24.4, 22.6, 22.5, 12.4. ESI mass m/z = 385 [M^+ + 1].

2.2.4. 4′-Dehydro-androst-4-eno[3,4-e]piperazin-6,17-dione 2d

Gum, yield 86%; IR cm^{-1}: 3385, 2944, 1737,1672, 1536, 1452, 1227; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.17 (bs, 1H, —NH), 3.52 (m, 2H, =N—CH_2—), 3.30 (m, 2H, —NH—CH_2—), 1.30 (s, 3H, 19—CH_3), 0.92 (s, 3H, 18—CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 221.1, 200.0, 171.1, 142.0, 124.5, 54.1, 51.2, 47.9 (2C), 39.0, 36.1, 36.0, 35.5, 34.2, 32.9, 31.6, 31.1, 22.1, 20.7, 17.7, 14.1. ESI mass m/z = 341 [M^+ + 1].

2.2.5. 4′-Dehydro-pregnan-4-eno[3,4-e]piperazin-6-one 2e

Gum, yield 85%; IR cm^{-1}: 3383 2941, 1702, 1583, 1539, 1450, 1275; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (bs, 1H, —NH), 3.78 (m, 2H, =N—CH_2—), 3.26 (m, 2H, —NH—CH_2—), 2.20 (s, 3H, 21—CH_3), 1.10 (s, 3H, 19—CH_3), 0.71 (s, 3H, 18—CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 209.5, 204.2, 167.1, 146.2, 117.1, 68.1, 65.2, 61.7, 58.3, 55.1, 54.2, 48.7, 43.4, 41.1, 39.5, 36.3 (2C), 28.9, 27.5, 26.8, 25.9, 19.0, 18.1. MS (ESI): ESI mass m/z = 369 [M^+ + 1].

2.2.6. 4′-Dehydro-24-ethyl-cholest-4,22-dieno[3,4-e]piperazin-6-one 2f

Brown crystals, yield 94%; mp: 207–210 °C; IR cm^{-1}: 3416, 2956, 1675, 1583, 1542, 1458, 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.09 (bs, 1H, —NH), 5.10 (m, 2H, —CH=CH—), 3.74, (m, 2H, =N—CH_2—), 3.20 (m, 2H, —NH—CH_2—), 1.09 (s, 3H, 19—CH_3), 0.75 (s, 3H, 18—CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 200.1, 167.6, 146.1, 142.9, 134.2, 117.7, 61.8, 60.53, 56.02, 55.3, 49.2, 47.1, 42.0, 41.2, 39.2, 36.7, 35.1, 32.74, 27.9, 27.2, 26.9, 25.9, 23.8, 22.6, 22.0, 21.8, 21.3, 19.7, 18.6, 17.1, 16.9. Mass m/z = 465 [M^+ + 1]. Anal calcd. for $C_{31}H_{48}N_2O$: C, 80.12; H, 10.41; N, 6.03. Found: C, 80.34; H, 10.22; N, 5.86.

3. Results and discussion

A number of approaches have been reported for the preparation of piperazine moiety, among them the most commonly described route utilizes the facile reaction of 1,2-diamine with 1,2-diketo compounds [20].

We carried out the reaction of 3-keto-4-en steroids using basic alumina as reaction medium under microwave irradiation [11] and isolating the product over silica gel by column chromatography. Under these conditions, 4-cholesten-3-one (**1a**) reacted with ethylenediamine to afford **2a** in 90% yield (Fig. 1). The product was characterized by spectral and analytical analysis. The ^{1}H NMR showed a downfield signal at δ 11.07 due to —NH proton and absence of the C-4 olefinic proton in the region δ 5.00–5.50. The ^{13}C NMR spectrum of **2a** exhibited characteristic signal for C-6 carbonyl carbon at δ 200.7, C-3 imine carbon at δ 163.5 and C-4 and C-5 olefinic carbons at δ 141.7 and 113.5, respectively. The ESI mass spectrum showed molecular ion peak at m/z 439 (M^+ + 1). We examined the feasibility of this synthetic route using other steroidal A-ring conjugated ketones such as testosterone (**1b**), testosterone acetate (**1c**), 4-androsten-3,17-dione (**1d**), progesterone (**1e**) and 24-ethyl-4,22-cholestadiene-one (**1f**) under identical conditions. In all cases, the reaction of **1a–f** with ethylene diamine afforded A-ring fused steroidal dehydropiperazines **2b–f** in high yields varying from 85% to 92%. When the reactions of **1a–f** were carried in solution using toluene under microwave, the products **2a–f** were obtained in 70–82% yield.

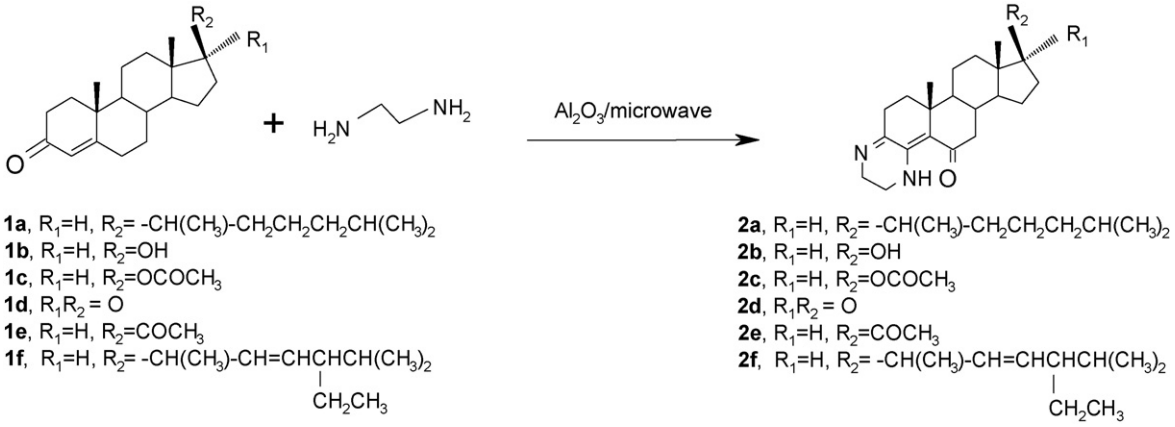

Fig. 1 – Synthesis of steroidal dehydropiperazines from corresponding steroidal conjugated carbonyl compounds.

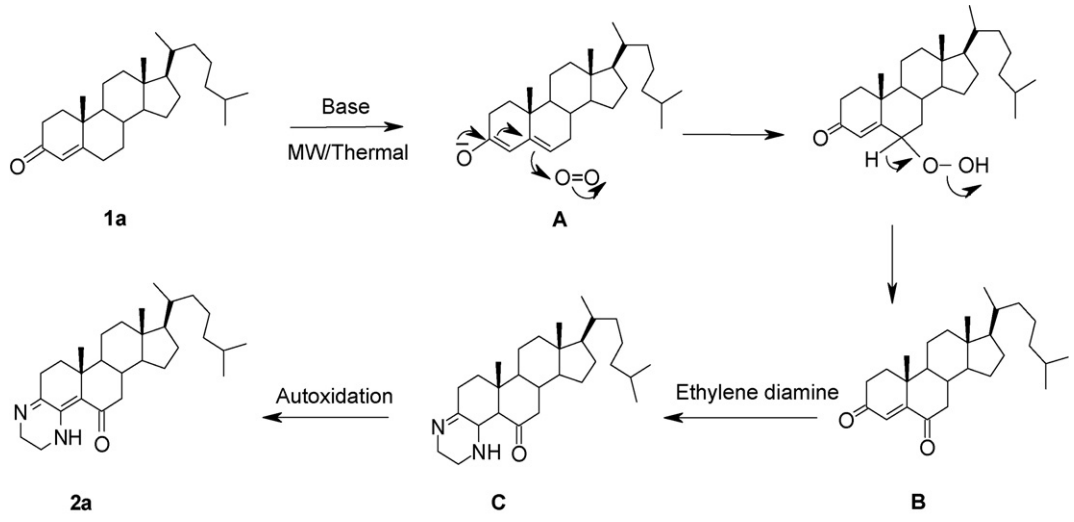

Fig. 2 – Proposed mechanism for the formation of dehydropiperazine derivative.

Similarly, 3-keto-4-en steroids **1a–f** reacted with ethylenediamine in refluxing toluene for 4–6 h to give A-ring steroidal dehydropiperazines **2a–f** in good yields (65–74%). Interestingly, dehydropiperazine adducts **2a–f** did not undergo aromatization reaction, as no pyrazine adducts could be isolated from the reaction mixtures.

A proposed mechanism for the formation of dehydropiperazine derivative **2a** from **1a** is shown in Fig. 2. Under the influence of basic ethylenediamine, the conjugated ketone initially facilitated arial oxidation [21,22] of the C-6 allylic protons via an enolate intermediate **A** to afford diketo intermediate **B**. The condensation of ethylenediamine with **B** followed by Michael addition and autoxidation led to **2a** via intermediate **C**. As a support to our presumption for the initial arial oxidation reaction, we treated 3-keto-cholest-4-en **1a** with *n*-butylamine instead of ethylenediamine, when it afforded 4-cholesten-3,6-dione (**B**) in high yield. The oxidation reaction of **1a** to **B** did not proceed under nitrogen atmosphere. Also, treatment of 4-cholesten-3,6-dione (**B**) [23] with ethylenediamine led to facile synthesis of **2a** in excellent yield. Further, the failure of **2a** to undergo aromatization under the reaction condition could be due to conjugation of the exocyclic enamino group with the carbonyl group of ring-B.

In conclusion, we have developed an efficient one-pot synthesis of A-ring steroidal dehydropiperazines from the reaction of 3-keto-4-en steroids with ethylenediamine in an environmentally benign condition. We have demonstrated that the reaction requires aerobic condition for the facile base catalysed conversion of mono keto steroid to diketo steroid. The methodology reported herein represents a new preparation of A-ring fused steroidal dehydropiperazines using easily available 3-keto-4-en steroids.

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