A microwave promoted and Lewis acid catalysed solventless approach to 4-azasteroids

Moyurima Borthakur, Romesh C. Boruah*
Medicinal Chemistry Division, North-East Institute of Science and Technology, Jorhat 785006, Assam, India

ARTICLE INFO
Article history:
Received 6 December 2007
Received in revised form
13 January 2008
Accepted 26 January 2008
Published on line 8 February 2008

Abstract
The preparation of 3-oxo-4-azasteroid from A-nor-3,5-secosteroid-3-oic acid is described in a solventless condition catalysed by Lewis acid under microwave irradiation. We utilized urea as an environmentally benign source for the generation of ammonia for the aza cyclization reaction.

© 2008 Elsevier Inc. All rights reserved.

1. Introduction

The replacement of one or more carbon atoms in a steroidal molecule by a nitrogen atom affects the chemical properties of the steroid and changes its biological activity [1]. The azasteroids thus accomplished received much attention during last few decades [2,3]. Among the large group of azasteroids are 4-aza lactams which exhibited 5α-reductase inhibitory property for the conversion of major circulating androgen testosterone to more active metabolite 5α-dihydrotestosterone. The most potent 5α-reductase inhibitor N-t-butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (finasteride) is used for treatment of benign prostatic hyperplasia, baldness and prostate cancer [4,5].

The preparation of finasteride has been reported mostly from 3β-hydroxy-5-pregnen-20-one (pregnenolone) or 4-androsten-3,17-dione in multi-step synthesis [6,7]. One of the key steps in the total synthesis of finasteride, is the construction of 3-oxo-4-azasteroid from A-nor-3,5-secoandrostan-3-oxo acid. However, the reported reaction conditions are often stringent as these employed either toxic reagents or harsh reaction conditions [8]. Consequently, the aza-cyclization reaction necessitates further attention for a safe and environmentally benign synthetic method.

The microwave promoted and solid-phase heterogeneous reaction is well-known as environmentally benign reaction methodology that usually provides improved selectivity, enhanced reaction rates, cleaner products and manipulative simplicity. We recently reported our efforts for the fast and facile reaction strategies that involve microwave energy as an unconventional energy source for three-component reaction [9]. We also succeeded in utilizing urea as a safe source of ammonia in the preparation of pyrimidines from β-formyl enamides under microwave irradiation [10].

Herein, we describe a convenient solid phase high yielding approach for the conversion of A-nor-3,5-secosteroid-3-oic acid to 3-oxo-4-azasteroid using urea as a facile source of...
ammonia catalysed by a Lewis acid under microwave irradiation.

2. Experimental

All reactions were carried in a solventless condition and monitored on Merck aluminium thin layer chromatography (TLC, UV254 nm) plates. Column chromatography was carried out on silica gel (60–120 mesh, Merck Chemicals). Melting points were determined in open capillary tubes on Buchi B-540 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR spectrometer using KBr pellets or on a thin film using chloroform. All the 1H and 13C NMR spectra were determined in open capillary tubes on Buchi B-540 apparatus. Chemical shifts values were given as δ ppm values. ESI mass spectra were recorded on a Brucker Daltonic Data Analysis 2.0 spectrometer.

2.1. The typical oxidation procedure

2.1.1. Synthesis of 5-oxo-A-nor-3,5-secocholestan-3-oic acid (1)

To a solution of 4-cholesten-3-one (3 g, 7.8 mmol) in isopropanol (40 ml) was added a solution of Na2CO3 (1.2 g, 36.18, 34.46, 32.00, 31.85, 30.12, 28.77, 28.59, 28.42 (2C), 24.57, 24.23, 23.25 (2C), 22.98, 21.31, 19.10, 12.35; MS (ESI): m/z 386 (M+1).

This procedure was followed for the synthesis of all products listed in Table 1.

2.2. 4-Aza-3-oxo-24-ethyl-cholest-5,22-dien (8)

Yield (880 mg 93%); mp 205–208 ºC; IR (cm−1): 3200, 2950, 1680, 1580, 1467, 1384, 1225; 1H NMR (CDCl3, 300 MHz): δ: 8.08 (1H, bs, –NH), 5.12–5.04 (2H, m, 22-H and 23-H), 4.94 (1H, s, 6-H), 1.01 (3H, s, 19-CH3), 0.73 (3H, s, 18-CH3), 2.65–0.61 (35H, m, alkane protons); 13C NMR (CDCl3, 300 MHz) δ: 170.00, 149.30, 147.72, 138.90, 126.29, 66.10, 65.36, 60.76, 57.47, 51.82, 50.04, 48.85, 43.61, 41.41, 41.12, 40.95, 39.24, 38.43, 34.95, 33.78, 30.66, 28.52 (2C), 28.24, 21.82, 21.66, 10.58 (2C); MS (ESI): m/z 412 (M+1).

2.2.2. 17β-Hydroxy-4-aza-3-oxo-androst-5-ene (9)

Yield (880 mg 84%); mp 289–291 ºC; IR (cm−1): 3345, 2945, 1675, 1565, 1456, 1387, 1220; 1H NMR (CDCl3, 300 MHz): δ: 8.07 (1H, bs, –NH), 4.85 (1H, s, 6-H), 3.63 (1H, s, 17-H), 1.07 (3H, s, 19-CH3), 0.75 (3H, s, 18-CH3), 2.45–0.70 (18H, m, alkane protons); 13C NMR (CDCl3, 300 MHz) δ: 170.31, 140.33, 103.93, 82.06, 51.49, 48.47, 43.29 (2C), 36.68, 34.64, 32.11, 31.91, 30.79, 29.73, 28.82, 23.77, 19.20, 11.53; MS (ESI): m/z 290 (M+1).

2.2.4. 17β-O-Acetoxy-4-aza-3-oxo-androst-5-ene (10)

Yield (850 mg 90%); mp 276–277.8 ºC; IR (cm−1): 3209, 2937, 1731, 1694, 1677, 1449, 1389, 1247; 1H NMR (CDCl3, 300 MHz): δ: 8.08 (1H, bs, –NH), 4.95 (1H, s, 6-H), 4.62 (1H, m, 17-H), 2.06 (3H, s, 17-COCH3), 1.10 (3H, s, 19-CH3), 0.83 (3H, s, 18-CH3), 2.48–0.80 (17H, m, alkane protons); 13C NMR (CDCl3, 300 MHz) δ: 176.06, 174.97, 144.63, 108.37, 87.32, 55.56, 52.62, 47.24 (2C), 41.18, 38.84, 36.18, 34.04, 33.10, 32.21, 28.23, 25.98, 25.17, 23.51, 16.80; MS (ESI): m/z 322 (M+1).

2.2.4. 4-Aza-3-oxo-pregn-5-ene (11)

Yield (863 mg 92%); mp 274–276 ºC; IR (cm−1): 3061, 2927, 1702, 1682, 1663, 1446, 1398, 1220; 1H NMR (CDCl3, 300 MHz): δ: 8.80 (1H, bs, –NH), 4.94 (1H, s, 6-H), 2.14 (3H, s, 20-CH3), 1.09 (3H, s, 19-CH3), 0.66 (3H, s, 18-CH3), 2.82–0.62 (18H, m, alkane protons); 13C NMR (CDCl3, 300 MHz) δ: 209.98, 170.60, 140.10, 104.03, 63.90, 56.98, 45.92, 44.42, 38.85, 34.37, 33.31, 31.98, 31.86, 29.98, 28.74, 24.77, 23.18, 21.07, 19.12, 13.73; MS (ESI): m/z 316 (M+1).

3. Results and discussion

We applied this method of using urea as a source of ammonia [11] on 5-oxo-A-nor-3,5-secocholester-3-olic acids (1–6) and obtained the corresponding 4-azasteroidal products (7–12) in excellent yields. As the experiments show, these azacyclization reactions...
Table 1 – Synthesis of 3-oxo-4-azasteroids using urea and BF₃·Et₂O under microwave irradiation

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="1" alt="Image" /></td>
<td><img src="7" alt="Image" /></td>
<td>95</td>
</tr>
<tr>
<td><img src="2" alt="Image" /></td>
<td><img src="8" alt="Image" /></td>
<td>93</td>
</tr>
<tr>
<td><img src="3" alt="Image" /></td>
<td><img src="9" alt="Image" /></td>
<td>84</td>
</tr>
<tr>
<td><img src="4" alt="Image" /></td>
<td><img src="10" alt="Image" /></td>
<td>90</td>
</tr>
<tr>
<td><img src="5" alt="Image" /></td>
<td><img src="11" alt="Image" /></td>
<td>92</td>
</tr>
<tr>
<td><img src="6" alt="Image" /></td>
<td><img src="12" alt="Image" /></td>
<td>90</td>
</tr>
</tbody>
</table>

Reactions are carried out in a solventless condition under microwave irradiation and catalysed by BF₃·Et₂O.

The 5-oxo-A-nor-3,5-secocholest-3,5-seco-cholestan-3-oic acids (1-6) could be derived from 4-cholesten-3-one, 24-ethyl-4-cholesten-5,22-dien-3-one, testosterone, testosterone acetate, progesterone and 4-androsten-3,17-dione via oxidation method using NaIO₄ and KMnO₄ in presence of Na₂CO₃ in excellent yields (80–86%). We employed isopropanol successfully as the reaction medium instead of tert-BuOH as reported in the literature [12].

In our approach, finely ground mixture of 5-oxo-A-nor-3,5-secocholest-3,5-seco-cholestan-3-oic acid (1) was irradiated in microwave with urea in presence of BF₃·Et₂O for 3 min after setting the reaction temperature at 140 °C and power 80% (maximum output 300 W). On completion of reaction (vide TLC), the reaction mixture was cooled and poured into water and

![Diagram](1-6) + NaIO₄/KMnO₄ → ![Diagram](7-12) + Urea/BF₃·Et₂O

Fig. 1 – Synthesis of 4-azasteroids using urea as a source of ammonia under microwave irradiation.
extracted with CH₂Cl₂. The organic portion was washed with water, dried over anhydrous Na₂SO₄ and the solvent was removed to obtain a crude product 7 in 95% yield. The product was characterized by spectral and analytical analysis. The ¹H NMR of 7 showed a broad singlet signal at δ 8.59 due to amide –NH proton and C-6 olefinic proton at δ 4.92. The ¹³C NMR spectrum of 7 exhibited characteristic signal for C-3 amide carbonyl carbon at δ 170.59, C-4 and C-5 olefinic carbons at δ 140.22 and 104.36, respectively. The ESI mass spectrum showed molecular ion peak at m/z 386 (M⁺+1). Similarly, 5-oxo-A-nor-24-ethyl-3,5-seco-22-cholesten-3-oic acid (2), 5-oxo-A-nor-3,5-seco-17β-hydroxy-androst-3-οic acid (3), 5-oxo-A-nor-3,5-seco-17β-acetoxy-androst-3-οic acid (4), 5-oxo-A-nor-3,5-seco-pregnan-3-οic acid (5), 5-oxo-A-nor-3,5-seco-androst-17-one-3-οic acid (6) and reacted with urea under identical condition to afford 4-azasteroids (8–12) in 84–93% yields (Fig. 1). However, the reaction of 5-oxo-A-nor-3,5-seco-steroid-3-οic acids (1–6) with urea and BF₃·Et₂O under conventional heating method (refluxing toluene) for 3–4 h failed to afford the desired 3-oxo-4-azasteroids (7–12).

In order to study the influence of the Lewis acid on the azacyclization reaction, we carried the solid-phase reaction of 1 independently with SmCl₃, ZrCl₄, TiCl₄, InCl₃ and AlCl₃ and obtained 2 in 60–80% yield. However, the reactions were found to be sluggish in absence of Lewis acid and the products were obtained in very poor yields (<15%).

A proposed mechanism for the formation of 3-oxo-4-azasteroid 7 from 1 is shown in Fig. 2. Under microwave heating urea released ammonia which reacted with 1 to afford imine intermediate (A). Tautomerization of intermediate (A) led to examine intermediate (B) under the reaction condition. Activation of the carboxyl group by BF₃·Et₂O led to the nucleophilic attack of the amino group to electron deficient carbonyl function facilitating aza cyclization with loss of water to afford 7. The catalytic role of Lewis acid in aza cyclization is evident from the fact that the reaction was sluggish in absence of Lewis acid with poor yield of the product.

In conclusion, we have developed a novel and efficient procedure for the preparation of 3-oxo-4-azasteroids from a solvent-less one-pot reaction of 5-oxo-A-nor-3,5-secocholestan-3-οic acid. The reaction was catalysed by various Lewis acids under microwave irradiation; however, BF₃·Et₂O gave the best result. We successfully demonstrated that urea can be used as an environmentally benign and safe source of ammonia avoiding liquid ammonia or toxic solvent [4]. In addition, the application of urea as a source of ammonia will become a feasible synthetic strategy and we believe that the expansion of this method will offer great benefit in organic synthesis.

Acknowledgements
We thank the Department of Science and Technology, New Delhi for financial support and CSIR, New Delhi for the award of a fellowship to one of us (MB). We also thank Director of this Institute for his keen interests.

References

