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

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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.

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-oic 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

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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, $UV_{254\,nm}$) 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 ^{13}C NMR spectra were recorded on Brucker Avance DPX 300 MHz spectrometer using tetramethylsilane (TMS) as internal standard. 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 Na_2CO_3 (1.2 g, 11.8 mmol) in water (6 ml). The mixture was brought to reflux and a solution of $NaIO_4$ (12 g, 56 mmol) and $KMnO_4$ (90 mg, 0.5 mmol) in warm water (75 °C) was added gradually (1 h) while reflux temperature was maintained. The reaction was cooled to 30 °C, and after 15 min the solids were removed by filtration. The solid was washed with water and the combined filtrates were concentrated under reduced pressure to remove most of the isopropanol. The aqueous residue was cooled and acidified (pH 3) with concentrated HCl solution. The product was extracted with CH_2Cl_2, washed with water and dried over anhydrous Na_2SO_4. Removal of the solvent afforded **1** (2.8 g, 89%) as a white solid.

2.2. *The typical azacyclization procedure*

2.2.1. *Synthesis of 4-aza-3-oxo-cholest-5-en (7)*

A mixture of **1** (1 g, 2.47 mmol) and urea (446 mg, 7.43 mmol) and $BF_3{\cdot}Et_2O$ (0.4 ml, 3.2 mmol) was mixed intimately in a mortar and irradiated in an open reaction vessel of a Synthwave 402 Prolabo focused microwave reactor (manufactured by M/S Prolabo, 54 rue Roger Salengro, Cedex, France) after setting the reaction temperature at 140 °C and power 80% (maximum output 300 W). On completion of reaction after 3 min (vide TLC), the reaction mixture was cooled and poured into water (50 ml) and extracted with CH_2Cl_2 (3× 30 ml). The organic portion was washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed to obtain a crude product. Column chromatography separation using EtOAc:Hexane (15:85) as eluant over silica gel afforded the title compound **7** (900 mg 95%); mp 232–35 °C; IR (cm^{-1}): 3193, 3050, 2950, 1683, 1670, 1467, 1384, 1225; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.59 (1H, bs, –NH), 4.92 (1H, s, 6-H), 1.08 (3H, s, 19-CH_3), 0.87 (3H, s, 18-CH_3), 2.46–0.70 (35H, m, alkane protons); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 170.59, 140.22, 104.36, 56.87, 56.46, 48.33, 42.81, 39.89, 36.54, 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.

2.2.2. *4-Aza-3-oxo-24-ethyl-cholest-5,22-dien (8)*

Yield (880 mg 93%); mp 205–208 °C; IR (cm^{-1}): 3200, 2950, 1680, 1665, 1460, 1385, 1225; ^1H NMR ($CDCl_3$, 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-CH_3), 0.73 (3H, s, 18-CH_3), 2.65–0.61 (35H, m, alkane protons); ^{13}C NMR ($CDCl_3$, 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).

2.2.3. *17β-Hydroxy-4-aza-3-oxo-androst-5-ene (9)*

Yield (880 mg 84%); mp 289–291 °C; IR (cm^{-1}): 3345, 2949, 1675, 1655, 1456, 1387, 1220; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.07 (1H, bs, –NH), 4.85 (1H, s, 6-H), 3.63 (1H, m, 17-H), 1.07 (3H, s, 19-CH_3), 0.75 (3H, s, 18-CH_3), 2.45–0.70 (18H, m, alkane protons); ^{13}C NMR ($CDCl_3$, 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 °C; IR (cm^{-1}): 3209, 2937, 1731, 1694, 1677, 1449, 1389, 1247; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.80 (1H, bs, –NH), 4.95 (1H, s, 6-H), 4.62 (1H, m, 17-H), 2.06 (3H, s, 17-$OCOCH_3$), 1.10 (3H, s, 19-CH_3), 0.83 (3H, s, 18-CH_3), 2.48–0.80 (17H, m, alkane protons); ^{13}C NMR ($CDCl_3$, 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* 332 (M^++1).

2.2.5. *4-Aza-3-oxo-pregn-5-ene (11)*

Yield (863 mg 92%); mp 274–276 °C; IR (cm^{-1}): 3061, 2927, 1702, 1682, 1663, 1446, 1398, 1220; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.80 (1H, bs, –NH), 4.94 (1H, s, 6-H), 2.14 (3H, s, 20-CH_3), 1.09 (3H, s, 19-CH_3), 0.66 (3H, s, 18-CH_3), 2.82–0.62 (18H, m, alkane protons); ^{13}C NMR ($CDCl_3$, 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).

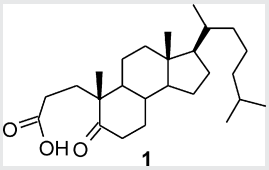
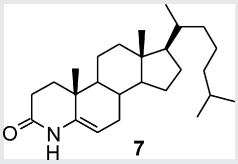
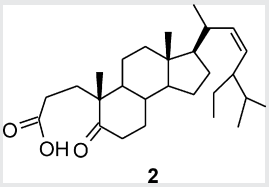
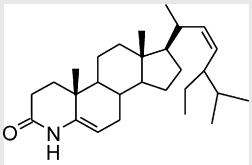
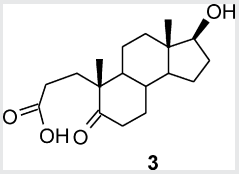
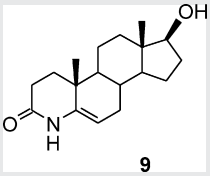
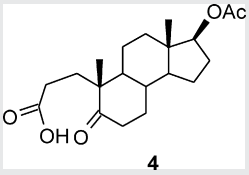
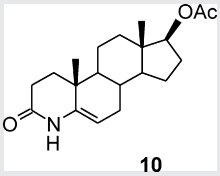
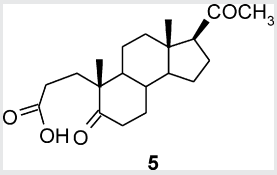
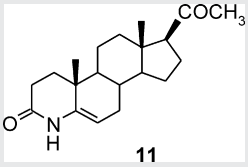
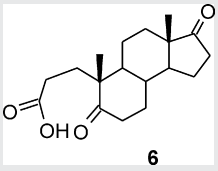
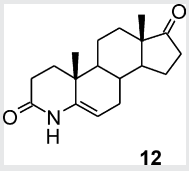
2.2.6. *4-Aza-androstan-5-en-3,17-dione (12)*

Yield (840 mg 90%); mp >300 °C; IR (cm^{-1}): 3189, 3066, 2944, 1737, 1677, 1663, 1451, 1389, 1212; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.70 (1H, bs, –NH), 4.97 (1H, s, 6-H), 1.12 (3H, s, 19-CH_3), 0.92 (3H, s, 18-CH_3), 2.50–1.06 (17H, m, alkane protons); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 221.18, 170.41, 140.45, 103.41, 51.87, 48.44, 48.03, 36.19, 34.60, 31.82, 31.64, 31.52, 29.03, 28.74, 22.20, 20.64, 19.17, 14.04; MS (ESI): *m/z* 288 (M^++1).

3. Results and discussion

We applied this method of using urea as a source ammonia [11] on 5-oxo-A-nor-3,5-secosteroid-3-oic acids (**1–6**) and obtained the corresponding 4-azasteroidal products (**7–12**) in excellent yields. As the experiments show, these azacyclization reac-

Table 1 – Synthesis of 3-oxo-4-azasteroids using urea and $BF_3{\cdot}Et_2O$ under microwave irradiation

Substrates	Products	Yield (%)
 1	 7	95
 2	 8	93
 3	 9	84
 4	 10	90
 5	 11	92
 6	 12	90

tions are carried in a solventless condition under microwave irradiation and catalysed by $BF_3{\cdot}Et_2O$.

The 5-oxo-A-nor-3,5-secosteroid-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 $NaIO_4$ and $KMnO_4$ in presence of Na_2CO_3 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-secocholestan-3-oic acid (**1**) was irradiated in microwave with urea in presence of $BF_3{\cdot}Et_2O$ 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

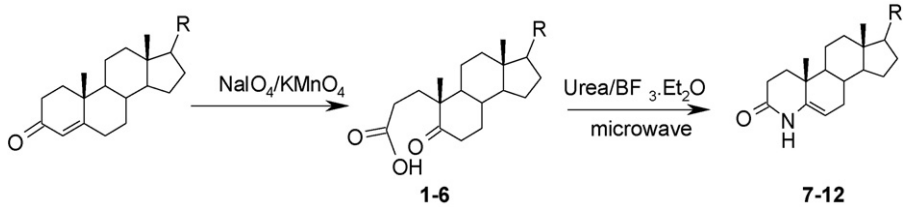


Fig. 1 – Synthesis of 4-azasteroids using urea as a source of ammonia under microwave irradiation.

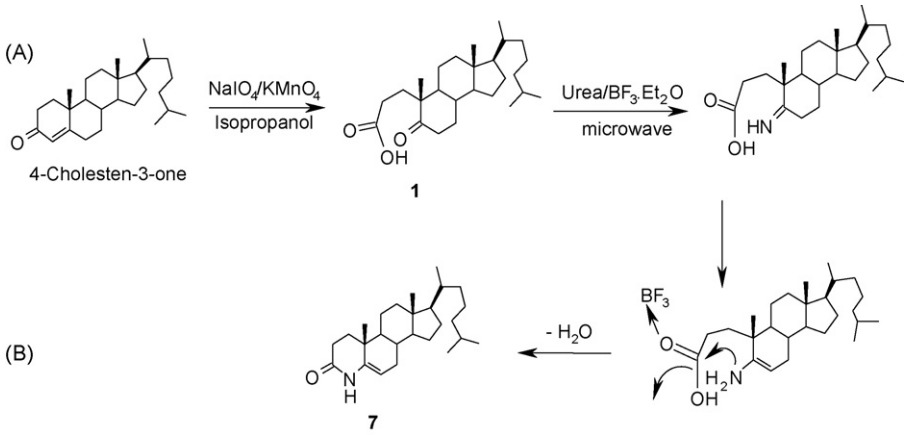


Fig. 2 – The suggested mechanism for Lewis acid catalysed azacyclization.

extracted with CH_2Cl_2. The organic portion was washed with water, dried over anhydrous Na_2SO_4 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 ^{13}C 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-androstan-3-oic acid (**3**), 5-oxo-A-nor-3,5-seco-17β-acetoxy-androstan-3-oic acid (**4**), 5-oxo-A-nor-3,5-seco-pregnan-3-oic acid (**5**), 5-oxo-A-nor-3,5-seco-androst-17-one-3-oic 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-secosteroid-3-oic acids (**1–6**) with urea and $BF_3{\cdot}Et_2O$ 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 $SmCl_3$, $ZrCl_4$, $TiCl_4$, $InCl_3$ and $AlCl_3$ 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 enamine intermediate (**B**) under the reaction condition. Activation of the carboxyl group by $BF_3{\cdot}Et_2O$ 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-oic acid. The reaction was catalysed by various Lewis acids under microwave irradiation; however, $BF_3{\cdot}Et_2O$ 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.

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