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Synthesis of 4-azasteroids by an intramolecular Ugi reaction

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ABSTRACT

In this paper we report the use of an intramolecular Ugi reaction to synthesize new 4-azacholestanes diversely substituted both at N-4 and C-5.

Both the scope and the stereochemical outcome of this approach were studied by varying the nature of the components necessary for this multicomponent reaction.

In sight of our results we concluded that this methodology can be applied to obtain 4-azasteroids targeted to find new biologically active compounds.

1. Introduction

The replacement of one or more carbon atoms of a steroid molecule by a heteroatom affects its chemical properties and often results in useful alterations to its biological activity. Azasteroids specially feature numerous biological activities [1]. Among the large and heterogeneous group of azasteroids, 4-azasteroids have attracted much interest, as many 4-azalactams exhibit strong inhibition of human steroid 5α-reductase, making them potential drugs for the treatment of benign prostatic hyperplasia [2]. Finasteride (**1**) and turosteride (**2**) are two commercial drugs belonging to this class (Fig. 1).

In addition, some 4-azasteroids, such as the cholestane derivative **3** (Fig. 1), have been shown to have interesting antifungal and antibacterial properties that are strongly dependent on the structural features of the studied compounds [3].

Taking the broad spectrum of biological properties of 4-azasteroids into account, our group started a research program devoted to the development of new synthetic strategies to achieve them. This strategy should be based on a simple and fast generation of new compounds having a high structural diversity. Multicomponent reactions are best suited to achieve this goal.

Multicomponent reactions (MCRs) are generally defined as reactions where more than two starting materials react to form a product, incorporating essentially all of the atoms of the educts. The structure of the reaction product can be easily diversified by a systematic variation of the starting materials [4].

One of the most versatile MCRs is the Ugi four-component reaction (U-4CR), which is based on the exceptional reactivity of the isocyanide functional group [5].

U-4CR constitutes a homogeneous group of reactions in which an amino component, an acid, a carbonyl compound and an isocyanide react together to give an α-aminoacylamide [4,5].

Intramolecular versions of the U-4CR, where two of the four functional groups involved belong to the same molecule, are particularly interesting for their ability to generate various heterocycles [6,7]. In this paper we report a new synthetic

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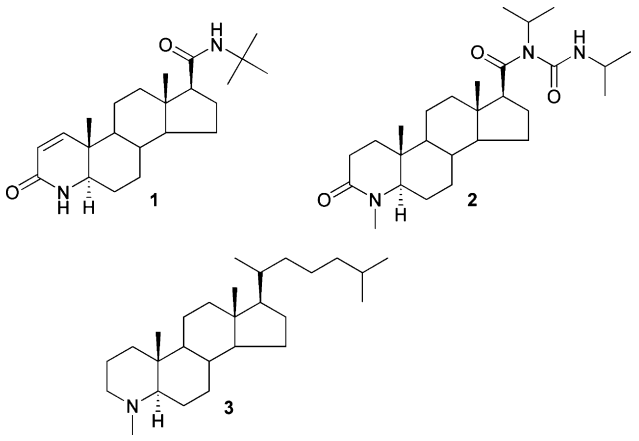

Fig. 1 – Examples of bioactive 4-azasteroids.

procedure to obtain 4-azasteroids, substituted at C-5, based on the intramolecular U-4CR between a bifunctional steroidal oxoacid and several amines and isocyanides.

2. Experimental

2.1. Synthesis

2.1.1. General

All the reagents were purchased from Sigma–Aldrich Chemical Co. EI-MS were measured either in a VG Trio-2 or in a Shimadzu QP-5000 mass spectrometer at 70 eV by direct inlet. Melting points were determined on a Fisher Johns apparatus and are uncorrected. All NMR spectra were recorded in $CDCl_3$ on a Bruker AM-500 (500 MHz for ^1H and 125.1 MHz for ^{13}C). Chemical shifts (δ) are given in ppm downfield from TMS as the internal standard. Coupling constant (J) values are in Hz. All solvents and reagents were of analytical grade.

All new compounds gave satisfactory NMR and mass spectral/combustion analysis data.

2.1.2. General synthetic procedure

The oxoacid **4** (5-oxo-A-nor-3,5-secocholestan-3-oic acid [8], 50 mg) was dissolved in methanol or ethanol and 1 equivalent of the corresponding amine was added. The mixture was stirred for 15 min at room temperature and 1 equivalent of the isonitrile was added. The reaction was refluxed for 16 h. The solvent was evaporated under reduced pressure and the residue was taken in EtOAc and washed with NaOH (5% aq). The mixture of epimers was separated by silica gel column chromatography (hexane/EtOAc gradient).

2.1.3. 4-Benzyl-5-N-(methoxycarbonylmethylen)-carboxamido-4-aza-5α-cholestan-3-one (**5a**)

M.p.: 177–178 °C. MS *m/z* (%): 606 (M^+, 0.1), 577 (0.5), 476 (97.2), 200 (20.9), 91 (100). ^1H NMR: 0.62 (18-H, 3H, s); 0.85 and 0.86 (26-H and 27-H, 3H, d, J = 2.3 Hz); 0.88 (H-21, 3H, d, J = 6.4 Hz); 0.92 (19-H, 3H, s); 2.62 (2-H, 2H, m); 3.68 and 3.87 ($NHCH_2COOCH_3$, 2H, dd, J = 5.7 and 17.7 Hz); 3.69 ($NHCH_2COOCH_3$, 3H, s); 4.66 and 4.91 (CH_2Ph, 2H, d, J = 14.8 Hz); 6.27 ($NHCH_2COOCH_3$, 1H, t, J = 5.7 Hz); 7.30 (CH_2Ph, 5H, m). ^{13}C NMR: 12.0 (C18); 16.0 (C19); 18.6 (C21); 22.0; 22.5 and 22.8 (C26 and C27); 23.8; 23.9; 26.7; 27.9; 28.2; 29.1; 29.3 (C2); 29.6; 33.6; 35.7; 36.1; 39.4; 39.7; 41.1 ($NHCH_2COOCH_3$); 41.4 (C10); 42.6 (C13); 43.9; 45.6 (CH_2Ph); 45.7; 52.2 ($NHCH_2COOCH_3$); 55.5; 56.0; 70.9 (C5); 127.3; 128.4; 128.7; 139.1; 169.9 ($CONHCH_2COOCH_3$); 173.7 (C3); 173.8 ($CONHCH_2COOCH_3$). Anal. Calcd. for $C_{38}H_{58}N_2O_4$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.33; H, 9.62; N, 4.59.

2.1.4. 4-Benzyl-5-N-(methoxycarbonylmethylen)-carboxamido-4-aza-5β-cholestan-3-one (**5b**)

M.p.: 155–156 °C. MS *m/z* (%): 606 (M^+, 0.2), 577 (0.5), 476 (95.2), 200 (22.9), 91 (100). ^1H NMR: 0.40 (7α-H, 1H, m); 0.62 (18-H, 3H, s); 0.86 and 0.87 (26-H and 27-H, 3H, d, J = 2.3 Hz); 0.89 (H-21, 3H, d, J = 6.4 Hz); 0.99 (19-H, 3H, s); 2.53 and 2.59 (2-H, 2H, m); 3.58 and 3.81 ($NHCH_2COOCH_3$, 2H, dd, J = 6.0 and 18.5 Hz); 3.67 ($NHCH_2COOCH_3$, 3H, s); 4.41 and 4.81 (CH_2Ph, 2H, d, J = 15.4 Hz); 6.33 ($NHCH_2COOCH_3$, 1H, t, J = 5.6 Hz); 7.26 (CH_2Ph, 5H, m). ^{13}C NMR: 11.9 (C18); 18.6 (C21); 19.4 (C19); 21.0; 22.5 and 22.8 (C26 and C27); 23.8; 26.2; 26.8; 27.4; 28.0; 28.2; 28.5 (C2); 34.0; 35.7; 36.1; 38.1 (C10); 39.5; 39.8; 41.5 ($NHCH_2COOCH_3$); 42.2; 42.3 (C13); 47.5 (CH_2Ph); 52.2 ($NHCH_2COOCH_3$); 56.1; 56.2; 73.8 (C5); 127.1; 128.2; 128.8; 138.5; 170.0 ($CONHCH_2COOCH_3$); 172.4 ($CONHCH_2COOCH_3$); 173.5 (C3). Anal. Calcd. for $C_{38}H_{58}N_2O_4$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.19; H, 9.70; N, 4.65.

2.1.5. 4-Benzyl-5-N-(diethoxyphosphorylmethylen)-carboxamido-4-aza-5α-cholestan-3-one (**6a**)

Colorless oil. MS *m/z* (%): 476 (M^+–$CONHPO(OEt)_2$, 0.3), 332 (1.2), 91 (8.4), 43 (100). ^1H NMR: 0.63 (18-H, 3H, s); 0.85 and 0.86 (26-H and 27-H, 3H, d, J = 2.5 Hz); 0.88 (H-21, 3H, d, J = 6.7 Hz); 0.92 (19-H, 3H, s); 1.33 and 1.37 ($NHCH_2PO(OCH_2CH_3)_2$, 6H, t, J = 7.1 Hz); 2.60 (2-H, 2H, m); 3.28 and 3.71 ($NHCH_2PO(OCH_2CH_3)_2$, 2H, ddd, J = 6.9, 11.6 and 15.8 Hz); 4.12 ($NHCH_2PO(OCH_2CH_3)_2$, 4H, m); 4.65 and 4.84 (CH_2Ph, 2H, d, J = 15.1 Hz); 6.07 ($NHCH_2PO(OCH_2CH_3)_2$, 1H, t, J = 5.7 Hz); 7.30 (CH_2Ph, 5H, m). ^{13}C NMR: 12.0 (C18); 16.0 (C19); 16.4 ($CONHCH_2PO(OCH_2CH_3)_2$, J = 6.0 Hz); 18.6 (C21); 22.1; 22.5 and 22.8 (C26 and C27); 23.8; 23.9; 26.7; 27.9; 28.2; 29.1; 29.2 (C2); 29.5; 33.6; 34.4 ($CONHCH_2PO(OCH_2CH_3)_2$, J = 154.6 Hz); 35.7; 36.1; 39.4; 39.7; 41.8 (C10); 42.6 (C13); 45.6 (CH_2Ph); 45.7; 55.6; 56.0; 62.3 and 62.5 ($CONHCH_2PO(OCH_2CH_3)_2$, J = 5.8 Hz); 71.0 (C5); 127.4; 128.3; 128.8; 139.0; 172.7 ($CONHCH_2PO(OCH_2CH_3)_2$, J = 3.1 Hz); 173.7 (C3). Anal. Calcd. for $C_{39}H_{63}N_2O_5P$: C, 69.82; H, 9.46; N, 4.18. Found: C, 69.95; H, 9.45; N, 4.20.

2.1.6. 4-Benzyl-5-N-(diethoxyphosphorylmethylen)-carboxamido-4-aza-5β-cholestan-3-one (**6b**)

Colorless oil. MS *m/z* (%): 476 (M^+–$CONHPO(OEt)_2$, 0.4), 332 (1.5), 91 (9.3), 43 (100). ^1H NMR: 0.45 (7α-H, 1H, m); 0.72 (18-H, 3H, s); 0.85 and 0.86 (26-H and 27-H, 3H, d, J = 2.4 Hz); 0.88 (H-21, 3H, d, J = 6.9 Hz); 0.99 (19-H, 3H, s); 1.31 and 1.35 ($NHCH_2PO(OCH_2CH_3)_2$, 3H, t, J = 7.0 Hz); 2.54 (2-H, 2H, m); 3.21 and 3.63 ($NHCH_2PO(OCH_2CH_3)_2$, 2H, ddd, J = 6.0, 13.0 and 17.1 Hz); 4.09 ($NHCH_2PO(OCH_2CH_3)_2$, 4H, m); 4.39 and 4.77 (CH_2Ph, 2H, d, J = 14.6 Hz); 6.11 ($NHCH_2PO(OCH_2CH_3)_2$, 1H, t, J = 6.0 Hz); 7.28 (CH_2Ph, 5H, m). ^{13}C NMR: 11.9 (C18); 16.4 ($CONHCH_2PO(OCH_2CH_3)_2$, J = 6.0 Hz); 18.6 (C21); 19.4 (C19); 21.0; 22.5 and 22.8 (C26 and C27); 23.8; 26.2; 26.8; 27.4; 28.0; 28.5 (C2); 34.0; 34.6 ($CONHCH_2PO(OCH_2CH_3)_2$, J = 150.0 Hz); 35.7; 36.1; 38.2 (C10); 39.5; 39.8; 42.3; 42.6 (C13); 47.4 (CH_2Ph); 56.0; 56.1; 62.3