Steroids 77 (2012) 521–527

Contents lists available at SciVerse ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Synthesis of [1,2,4]-triazolo-annulated 3-aza-A-homocholestanes—A novel class of pentacyclic compounds

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ARTICLE INFO

Article history:
Received 10 November 2011
Received in revised form 18 January 2012
Accepted 22 January 2012
Available online 31 January 2012

Keywords:
5α-Cholestan-3-one
3-Aza-A-homocholestanes
1,3-Dipolar cycloaddition
Ring expansion

ABSTRACT

This study was performed to investigate the reactivity of azocarbenium salts derived from 5α-cholestan-3-one towards 1,3-dipolar cycloaddition reactions with inverse electron-demand to produce unprecedented steroidal heterocyclic derivatives, i.e. [1,2,4]-triazolo-annulated 3-aza-A-homocholestanes **8** and **11** and picrates **12**. The synthetic steps were comprised of oxidizing hydrazones **3** with *tert*-butyl hypochlorite to germinal chloroazo compounds **4**, generation of the 1-aza-2-azoniaallene cations **5** by action with equimolar antimony pentachloride and interception with nitrile and alkyne molecules by cycloaddition to the triple bond followed by ring enlargement. The structure of the compounds was principally established on the basis of the analytical and spectral data along with the previously published X-ray diffraction analysis on **8a**.

1. Introduction

Steroid heterocycles have interesting biological activities [1–3]. The replacement of one or more carbon atoms in a steroid molecule by a heteroatom, especially nitrogen often results in useful alterations of its biological activity [4]. On the other hand, azepine compounds with an additional triazolo ring fused on the seven-membered ring possess a wide spectrum of important biological properties, such as anti-tumor agents [5], selective inhibition of 11β-hydroxysteroid dehydrogenase [6], the reduction of beta-amyloid protein production [7], and even herbicidal activity [8]. In general, the fusion of a triazolo ring plays a vital role in enhancing the affinities for receptors. To the best of our awareness, available methods for achieving the expansion of the steroidal A-ring to an azepine ring seem to be scarce. The most exploited strategies are the Schmidt reaction [9,10] and the Beckmann rearrangement [11,12].

In recent years, we have been engaged in a program toward synthesizing novel triazolo annulated heterocycles. We have established a reliable synthetic pathway to [1,2,4]triazolo[3,2-*d*][1,5]benzoxazepines and their chalcogen analogs starting from chroman-4-ones and thiochroman-4-ones [13,14]. We have also successfully applied the protocol to the synthesis of novel thieno[2,3-*f*][1,2,4]triazolo[1,5-*a*]azepines, furo[3,2-*c*][1,2,4]triazolo[1,5-*a*]azepinium salts and furo[2,3-*f*][1,2,4]triazolo[1,5-*a*]azepinum picrates by starting from the appropriate bicyclic ketones [15,16]. Quite recently, we have also successfully employed this strategy to achieve a hitherto unknown 1,2,4-triazolo-fused steroidal azepine compound from 5α-cholestan-3-one [17].

In continuation of our long-standing interests on this topic, we report herein the detailed study on the synthesis of this class of novel 1,2,4-triazolo-fused steroidal azepine compounds. The synthetic genre shares a common mechanistic scenario: the key step employs the cycloaddition of 1-aza-2-azoniaallenium ions, positively charged four-electron, three-center 1,3-dipoles, to the triple bond of unsaturated compounds followed by ring enlargement and insertion of a nitrogen atom to furnish the pentacyclic products.

2. Experimental

2.1. General remarks

All commercial materials were used without further purification. Solvents were purified and dried by standard methods prior to use. Reactions were monitored by thin layer chromatography (TLC) on Silica Gel 60 F_{254} (Fluka). Infrared spectra were recorded as KBr disks on a Nicolet-360 IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solutions on a JEOL ECA 400 or a Bruker AMX 500 spectrometer using TMS as an internal reference and reported in ppm (δ). Coupling constant (J) values are given in Hz. Multiplicity are expressed as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Elemental analysis for C, H, N was performed on CAPLO ERBA1106 elemental analyzer. High resolution mass spectra (HRMS) were recorded on a SHIMADZU LCMS-IT-TOF mass spectrometer with ESI ionization. Melting points were determined in open capillary tubes and are uncorrected.

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doi:10.1016/j.steroids.2012.01.016

2.2. Organic synthesis

2.2.1. General experimental procedure for the synthesis of 5α-cholestan-3-one hydrazones

Equimolar amounts of 5α-cholestan-3-one **1** (1.93 g, 5 mmol) and hydrazine **2a** or hydrazide **2b** (5 mmol) in EtOH (20 mL) containing HOAc (0.1 mL) were heated under reflux for 3 h and then left to cool. The solid product **3** formed upon cooling at room temperature was collected by filtration and crystallized from hot EtOH (95%).

2.2.2. 5α-Cholestan-3-one (2,4,6-trichlorophenyl)hydrazone (**3a**)

The physical data and spectral data for **3a** were published previously (Ref. [17]).

2.2.3. 5α-Cholestan-3-one (N-ethoxycarbonyl)hydrazone (**3b**)

From 5α-cholestan-3-one **1** and ethyl carbazate **2b**. Yield 2.20 g (93%); white solid; mp 99–100 °C. IR (KBr): ν 3280, 1715, 1557, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.66–2.52 (m, 49H, steroidal H & $CO_2CH_2CH_3$), 4.27 (q, J = 6.1 Hz, 2H, $CO_2CH_2CH_3$), 7.62 (s, 1H, NH). *Anal.* required for $C_{30}H_{52}N_2O_2$ (%): C, 76.22; H, 11.09; N, 5.93. Found: C, 76.33; H, 10.95; N, 5.95.

2.2.4. Preparation of the α-chloroazo substrates (**4a**,**b**): general procedure

The reaction was carried out in the dark with exclusion of moisture. A solution of *t*-BuOCl (0.19 g, 1.5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to an ice-water cooled solution of hydrazone **3** (1 mmol) in dry CH_2Cl_2 (10 mL) over 10 min. The mixture was stirred for 15–30 min, and the reaction was monitored by TLC. After the reaction went to completion, anhydrous $CaCl_2$ was added to the resultant yellow solution. Substrates **4** could not be purified without partial decomposition, and therefore the solution containing **4** was used for next reaction. The solution can be stored at <4 °C in the dark for <24 h.

2.2.5. General procedure for the synthesis of the triazolo-fused 3-aza-A-homocholestanes **8a**–**f** and pyrazolo-fused analog **8g**

The reaction was carried out in a nitrogen atmosphere. The solution containing the chloride **4** was filtered. To the filtrate was added dropwise the appropriate triple bond compound **6** (nitrile or 1-ethynylbenzene, 1.5 mmol). The reaction mixture was cooled between −70 and −60 °C. A solution of $SbCl_5$ (0.37 g, 1.2 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to the mixture over a period of 0.5 h. After being stirred for 2 h between −60 and −30 °C, the mixture was allowed gradually to warm to 30 °C (bath temperature) and stirred for additional 1.5 h. Different solvent or solvent combinations should be used depending on solubility of individual product (see below). This afforded five-membered ring annulated 3-aza-A-homocholestanes **8a**–**g**. Yields were calculated based on the employed hydrazone **3**.

2.2.6. [1R-[1α(R*),3aβ,3bα,5aβ,12aα,12bβ,14aα]]-1-(1,5-dimethylhexyl)-1,2,3,3a,3b,4,5,11,12,12a,12b,13,14,14a-tetradecahydro-8,12a,14a-trimethyl-9-(2,4,6-trichlorophenyl)-cyclopenta[5,6]naphtho[2,1-d][1,2,4]triazolo[1,5-a]azepinium hexachloroantimonate (**8a**)

The physical data and spectral data for **8a** were published previously (Ref. [17]).

2.2.7. [1R-[1α(R*),3aβ,3bα,5aβ,12aα,12bβ,14aα]]-1,2,3,3a,3b,4,5,11,12,12a,12b,13,14,14a-tetradecahydro-12a,14a-dimethyl-1-(1,5-dimethylhexyl)- 8-propyl-9-(2,4,6-trichlorophenyl)-cyclopenta[5,6]naphtho[2,1-d][1,2,4]triazolo[1,5-a]azepinium hexachloroantimonate (**8b**)

From hydrazone **3a** and butyronitrile. Upon completion of the reaction, all volatiles were removed by distillation under high vacuum, the green residue was recrystallized from MeOH and then from MeOH–MeCN (v/v 5:1) twice to afford pure **8b**. Yield 0.29 g (30%); brown powder; mp 170–172 °C. IR (KBr): ν 2933, 2868, 1560, 1556, 1457, 1386 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.65–2.50 (m, 47H, steroidal H & $CH_2CH_2CH_3$), 2.55 (t, J = 7.1 Hz, 2H, $CH_2CH_2CH_3$), 3.00 (m, 1H, H_c), 3.33 (m, 1H, H_d), 4.10 (m, 1H, H_a), 4.37 (m, 1H, H_b), 7.73 (s, 2H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 12.1, 18.7, 21.3, 22.6, 22.8, 23.82, 24.09, 28.0, 28.2, 28.4, 28.5, 30.3, 31.1, 31.5, 34.6, 34.8, 35.7, 36.1, 37.4, 39.5, 39.6, 39.7, 42.2, 43.7, 45.1, 46.2, 52.6, 56.2, 56.3 (steroidal & *n*-Pr), 122.4, 130.8, 131.1, 135.6, 136.6, 143.0 (Ar)), 162.6, 163.9 (C=N). HRMS (ESI): m/z calcd. for the cation $[C_{37}H_{55}Cl_3N_3]^+$: 646.3462; found: 646.3440.

2.2.8. [1R-[1α (R*),3aβ,3bα,5aβ,12aα,12bβ,14aα]]-8-benzyl-1-(1,5-dimethylhexyl)-1,2,3,3a,3b,4,5,11,12,12a,12b,13,14,14a-tetradecahydro-12a,14a-dimethyl-9-(2,4,6-trichlorophenyl)-cyclopenta[5,6]naphtho[2,1-d][1,2,4]triazolo[1,5-a]azepinium hexachloroantimonate (**8c**)

From hydrazone **3a** and phenylacetonitrile. Work-up as described above furnished **8c**. Yield 0.34 g (33%); brown powder; mp 140–142 °C. IR (KBr): ν 2929, 1627, 1562, 1449, 1385, 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.66–2.50 (m, 42H, steroidal H), 3.02 (m, 1H, H_c), 3.31 (m, 1H, H_d), 4.05 (s, 2H, Ph-CH_2), 4.11 (m, 1H, H_a), 4.30 (m, 1H, H_b), 7.00–7.29 (m, 5H, Ph), 7.65 (s, 2H, $Cl_3C_6H_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.0, 18.6, 21.4, 22.5, 22.8, 23.8, 24.0, 24.1, 28.0, 28.2, 29.7, 30.3, 31.5, 33.9, 34.2, 34.6, 34.8, 35.7, 36.1, 39.5, 39.8, 42.2, 43.9, 52.8, 56.2, 56.3 (steroidal & $PhCH_2$), 122.6, 128.6, 129.2, 129.3, 130.3, 130.8, 131.4, 135.9 (Ar), 160.6, 163.3 (C=N). HRMS (ESI): m/z calcd. for the cation $[C_{41}H_{55}Cl_3N_3]^+$: 694.3462; found: 694.3480.

2.2.9. [1R-[1α(R*),3aβ,3bα,5aβ,12aα,12bβ,14aα]]-8-(2-(bromomethyl)phenyl)-1-(1,5-dimethylhexyl)-1,2,3,3a,3b,4,5,11,12,12a,12b,13,14,14a-tetradecahydro-12a,14a-dimethyl-9-(2,4,6-trichlorophenyl)-cyclopenta[5,6]naphtho[2,1-d][1,2,4]triazolo[1,5-a]azepinium hexachloroantimonate (**8d**)

From hydrazone **3a** and *o*-(bromomethyl)benzonitrile. Work-up as described above furnished **8d**. Yield 0.99 g (89%); pale-brown powder; mp 154–156 °C. IR (KBr): ν 2937, 2866, 1568, 1464, 1382 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.66–2.43 (m, 42H, steroidal H), 3.16 (m, 1H, H_c), 3.49 (m, 1H, H_d), 4.26 (m, 1H, H_a), 4.59 (m, 1H, H_b), 4.76–4.87 (m, 2H, BrCH_2), 7.10–7.73 (m, 6H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.0, 18.6, 21.3, 22.6, 22.8, 23.8, 24.1, 28.0, 29.3, 31.5, 34.8, 36.1, 39.5, 39.7, 42.2, 43.8, 52.8, 56.2 (steroidal & CH_2Br), 120.9, 123.7, 128.6, 129.2, 130.8, 131.2, 133.3, 134.0, 142.8 (C_6H_4, $Cl_3C_6H_2$), 158.8, 163.1 (C=N). HRMS (ESI): m/z calcd. for the cation $[C_{41}H_{54}BrCl_3N_3]^+$: 772.2567; found: 772.2579.

2.2.10. [1R-[1α(R*),3aβ,3bα,5aβ,12aα,12bβ,14aα]]-1-(1,5-dimethylhexyl)-1,2,3,3a,3b,4,5,11,12,12a,12b,13,14,14a-tetradecahydro-12a,14a-dimethyl-9-(2,4,6-trichlorophenyl)-8-vinyl-cyclopenta[5,6]naphtho[2,1-d][1,2,4]triazolo[1,5-a]azepinium hexachloroantimonate (**8e**)

From hydrazone **3a** and acrylonitrile. Work-up as described above furnished **8e**. Yield: 0.90 g (93%); pale-yellow powder; mp 192–194 °C. IR (KBr): ν 2934, 2866, 1569, 1560, 1477, 1460, 1390 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.66–2.43 (m, 42H, steroidal H), 3.00 (m, J = 16.5 Hz, 1H, H_c), 3.35 (m, J = 16.0 Hz, 1H, H_d),