Steroids 109 (2016) 1–6

Contents lists available at ScienceDirect

Steroids

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

An expedient sequential one-pot four component synthesis of novel steroidal spiro-pyrrolidine heterocycles in ionic liquid

D. Gavaskar [a,1], A.R. Suresh Babu [b,1], R. Raghunathan [a,*], M. Dharani [c], S. Balasubramanian [c]

[a] Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, India
[b] Institute of Molecular and Cellular Biology (IBMC), University of Strasbourg, Strasbourg, France
[c] Department of Inorganic Chemistry, University of Madras, Guindy Campus, Chennai, India

ARTICLE INFO

Article history:
Received 14 August 2015
Received in revised form 4 February 2016
Accepted 12 February 2016
Available online 27 February 2016

Keywords:
Estrone
Ionic liquid
Azomethine ylide
Cycloaddition
Indenoquinoxaline
Steroidal pyrrolidine

ABSTRACT

A facile one-pot synthesis of novel steroidal dispiro-indenoquinoxaline pyrrolidines *via* multicomponent-[3+2]-cycloaddition of azomethine ylides in ionic liquid is described. The structure of cycloadduct is confirmed by IR, ^{1}H NMR, ^{13}C NMR, high resolution mass spectroscopy and elemental analysis.

1. Introduction

Steroids form a group of structurally related compounds widely distributed in nature and possess a broad spectrum of biological activities. Synthetic steroidal derivatives have captured a good deal of attention for developing lead compounds to treat several diseases. Particularly, the synthesis of steroid containing heterocycles has received much attention of the chemist due to their significant pharmacological properties [1]. Such steroid based compounds turn out to be nontoxic, less vulnerable to multi-drug resistance (MDR) and highly bioavailable because of being capable of penetrating the cell wall [2]. Steroids find widespread applications as anti-inflammatory, diuretic, anabolic, contraceptive, antiandrogenic, and anticancer agents [3]. Many of the steroidal heterocycles have been found to exhibit potent biological activities, such as anti-inflammatory, anabolic, anti-cancer and anti-microbial activities [4–11]. Recently, heterocyclic estrone derivatives have been found to exhibit potential antibacterial, antifungal and antiproliferative activities [12]. Synthesis of novel pharmacological agents with minimum number of steps and less time is a major challenge for chemists. Conventional approach uses multistep reaction sequences which are typically associated with low yields, high cost and tedious isolation and purification of the resulting products. Multicomponent reactions (MCRs) offer a valuable solution for such a situation for the synthesis of complex heterocyclic compounds [13]. Ionic liquids are emerging as a set of new green solvents to replace the volatile organic solvents as they are ecological, economical, non-volatile and offer new robust chemical and physical properties, such as high thermal and chemical stability, very low to negligible vapor pressure and good solvating ability. In recent years, ionic liquids have attracted increasing interest as recyclable solvents, catalysts and reagents owing to their green credentials and tunable properties [14].

The intermolecular [3+2]-cycloaddition reaction of azomethine ylides with various alkenes and alkynes represents an efficient and convergent method for the construction of biologically active pyrrolidine and pyrrolizidine units [15]. Pyrrolidine derivatives are very useful in preventing and treating rheumatoid arthritis, asthma, allergies and related diseases as they inhibit the production of prostaglandin E2 and intracellular phospholipase A2 [16] and they also possess anti-influenza [17], anti-convulsant [18] and anti-tumor activities [19]. Quinoxaline derivatives are an important class of biologically active nitrogen containing heterocycles emerging as an attractive target of extensive research due to their inherent diverse properties [20]. Spiro compounds constitutes a vital group of many naturally occurring compounds identified by their highly pronounced biological properties [21]. Spiro steroids are frequently found in nature, such as spirostanes with

* Corresponding author.
E-mail address: ragharaghunathan@yahoo.com (R. Raghunathan).
[1] These authors contributed equally to the work.

http://dx.doi.org/10.1016/j.steroids.2016.02.010
0039-128X/

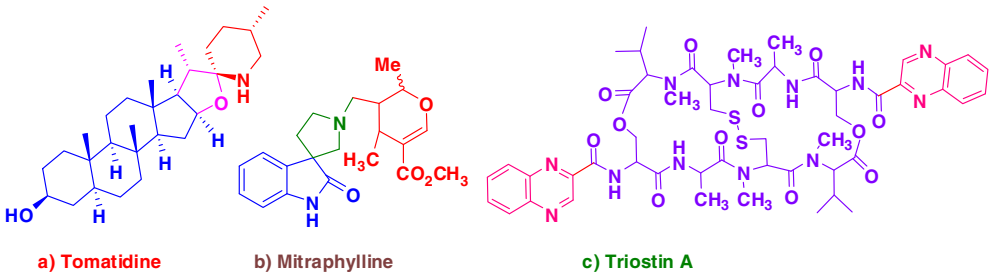

Fig. 1. Some of the naturally occurring biologically active (a) spiro-steroidal heterocycle, such as Tomatidine (b) spiro-pyrrolidine such as Mitraphylline and (c) quinoxaline derivative such as Triostin A.

a spiroacetal moiety in the structure and show significant biological activities [22]. Some of the naturally occurring biologically significant spiro-steroids, spiro-pyrrolidine and quinoxaline derivatives are shown in Fig. 1.

2. Experimental

All melting points were uncorrected. IR spectra were recorded on a SHIMADZU 8300 series FT-IR instrument. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a BRUKER 300 spectrometer at 300 MHz. Chemical shifts are given in parts per million (d-scale) and the coupling constants are given in Hertz. ^{13}C NMR was recorded on a BRUKER 300 spectrometer at 75 MHz. High resolution mass spectra were recorded on a JEOL-GC-MATE II mass spectrometer (70 Energy eV, Quadrapole double focusing mass analyzer with photomultiplier tube detector). Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Column chromatography was performed on silica gel (ACME, 100–200 mesh). Routine monitoring of the reactions was made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 0.25 mm thickness and visualized with iodine. Silica gel-G plates (Merck) were used for tlc analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. The starting materials estrone, 1,2-phenylenediammine, ninhydrin and sarcosine were purchased commercially and used as such.

2.1. General procedure for the synthesis of steroidal dispiro-pyrrolidine 5a

A mixture of ninhydrin **2** (1 mmol) and 1,2-phenylenediamine **3** (1 mmol) was stirred for 10 min in 5 mL of ionic liquid **7** at 120 °C. To this mixture, sarcosine **4** (1 mmol) and (*Z*)-16-benzylidene estrone **1a** (1 mmol) in 5 mL of ionic liquid **7** was added. The mixture was heated at 120 °C with stirring in an oil bath until completion of the reaction as evidenced by TLC. After the completion of the reaction, cold water (3 mL) was added to the reaction mixture and the crude product was filtrated, dried under vacuum and purified by column chromatography using petroleum ether/ethyl acetate (4:1) as eluent. The ionic liquid was then dried under reduced pressure at 100 °C for 1–2 h to remove any water trapped and TLC analysis of the recovered ionic liquid showed the absence of any starting material and product, hence reused for subsequent runs.

2.1.1. 1-N-methyl-spiro[2′,11″]-indeno[1,2-b]quinoxaline-spiro [3′,16]-estrone-4′-phenyl-pyrrolidine ***5a:***

Color: Pale yellow; Eluent: petroleum ether/ethyl acetate (4:1); R_f value: 0.5; IR (KBr cm^{-1}): 3455 (–OH), 1736 (–C=O), 1581 (–C=N); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 0.50 (s, 3H, 18-CH_3), 0.83–1.69 (m, 11H), 2.00 (s, 3H, –NCH_3), 2.17–2.20 (m, 2H), 2.35 (s, 3H, Ar–CH_3), 3.73–3.78 (t, J = 16.8 Hz, 1H), 4.22–4.27 (t, J = 17.7 Hz), 4.37–4.43 (t, J = 18.9 Hz) 6.30 (s, 1H), 6.58 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 7.8 Hz, 2H), 7.45–7.63 (m, 5H), 7.71–7.84 (m, 3H), 8.11–8.16 (t, J = 8.4 Hz, 2H), 8.32 (d, J = 7.5 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.23, 21.12, 22.66, 25.99, 29.01, 29.70, 31.25, 32.25, 34.42, 36.68, 43.98, 47.10, 51.35, 61.79, 69.66, 78.73, 113.05, 114.68, 122.37, 126.17, 128.55, 129.39, 129.84, 129.99, 130.33, 130.92, 131.84, 136.54, 136.94, 137.82, 140.87, 147.12, 153.58, 154.27, 163.36, 193.37 ppm; HRMS *m*/*z*: calculated 617.9781; found: 617.9780 (M$^+$); *CHN* analysis calculated for $C_{42}H_{39}O_2N_3$: C, 81.63; H, 6.36; N, 6.79; Found: C, 81.49; H, 6.52; N, 6.91%.

2.1.2. 1-N-methyl-spiro[2′,11″]-indeno[1,2-b]quinoxaline-spiro [3′,16]-estrone-4′(4′-methylphenyl)-pyrrolidine ***5b:***

Color: Pale yellow; Eluent: petroleum ether/ethyl acetate (4:1); R_f value: 0.5; IR (KBr cm^{-1}): 3418 (–OH), 1728 (–C=O), 1582 (–C=N); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 0.52 (s, 3H, 18-CH_3), 0.76–2.17 (m, 11H), 1.99 (s, 3H, –NCH_3), 2.35 (s, 3H, Ar–CH_3), 3.73–3.78 (t, J = 8.4 Hz, 1H), 4.22–4.27 (t, J = 9.60 Hz, 1H), 4.37–4.43 (t, J = 9.30 Hz), 6.0 (s, 1H), 6.30–6.31 (d, J = 2.1 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 7.17–7.25 (m, 2H), 7.47–7.54 (m, 3H), 7.56–7.63 (m, 5H), 7.73–7.81 (m, 2H), 8.14–8.16 (t, J = 6.0 Hz, 2H), 8.33 (d, J = 7.33 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.23, 21.12, 22.66, 25.98, 29.01, 29.70, 31.25, 32.25, 34.42, 36.68, 43.98, 47.10, 51.35, 61.79, 69.66, 78.73, 113.05, 114.68, 122.37, 126.16, 128.55, 129.39, 129.84, 130.26, 130.33, 130.92, 131.84, 136.54, 136.94, 137.35, 137.83, 140.87, 147.12, 153.58, 154.27, 163.36, 193.37 ppm; HRMS *m*/*z*: calculated 631.9865; found: 631.9864 (M$^+$); *CHN* analysis calculated for $C_{43}H_{41}O_2N_3$: C, 81.78; H, 6.57; N, 6.85; Found: C, 81.66; H, 6.68; N, 7.05%.

2.1.3. 1-N-methyl-spiro[2′,11″]-indeno[1,2-b]quinoxaline-spiro [3′,16]-estrone-4′(4‴-methoxyphenyl)-pyrrolidine ***5c:***

Color: Pale yellow; Eluent: petroleum ether/ethyl acetate (4:1); R_f value: 0.5; IR (KBr cm^{-1}): 3448 (–OH), 1728 (–C=O), 1586 (–C=N); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 0.50 (s, 3H, 18-CH_3), 0.83–2.28 (m, 11H), 1.25 (s, 3H, –NCH_3), 3.72–3.87 (m, 2H), 3.87 (s, 3H, OMe), 4.20–4.26 (t, J = 9.3 Hz 1H, –NCH_2), 4.35 (t, 9.3 Hz, 1H), 6.31 (bs, 1H), 6.59 (d, J = 6.0 Hz, 1H), 6.89 (d, J = 6.6 Hz, 1H), 6.95 (s, 1H), 7.45–7.66 (m, 5H), 7.72–7.85 (m, 2H), 8.05 (d, J = 8.7 Hz, 1H), 8.12–8.16 (t, J = 6.6 Hz 2H), 8.32–8.39 (d, J = 8.1 Hz 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.18, 22.66, 26.00, 29.04, 31.24, 32.25, 34.41, 36.72, 43.97, 47.14, 51.07, 55.23, 61.86, 69.69, 78.75, 113.14, 113.72, 113.82, 114.66, 122.42, 126.19, 128.52, 129.35, 129.45, 129.84, 130.85, 131.42, 132.03, 137.33, 137.78, 140.87, 147.10, 153.55, 154.36, 158.55, 163.44 ppm; HRMS *m*/*z*: calculated 637.6328; found: 637.6327 (M$^+$); *CHN* analysis calculated for $C_{43}H_{41}O_3N_3$: C, 81.63; H, 6.36; N, 6.79; Found: C, 81.79; H, 6.22; N, 6.91%.