STEROIDS 73 (2008) 375–407

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

Review

Recent advances in azasteroids chemistry

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ARTICLE INFO

Article history:
Received 8 October 2007
Received in revised form
10 December 2007
Accepted 13 December 2007
Published on line 4 February 2008

Keywords:
Azasteroid
Biological activity

ABSTRACT

Modified steroids have attracted a great deal of attention these last years. Their preparation is a stimulating challenge to the organic chemist, often demanding development of new and generally useful reactions. Moreover, the biological properties of modified steroids have proved to be of interest. The recent development in the partial and total syntheses of azasteroids is herein described.

Contents

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doi:10.1016/j.steroids.2007.12.013

1. Introduction

The steroid system, selected by the evolutionary process to perform some of the most fundamental biological functions, has not only inspired biochemists and endocrinologists, but also has become the basis of many important discoveries in organic chemistry.

The replacement of one or more carbon atoms of a steroid molecule by a heteroatom affects the chemical properties of a steroid and often results in useful alterations to its biological activity. The potential of heterosteroids in general, and azasteroids in particular, as novel drugs and the challenge of their synthesis prompted numerous research groups to undertake studies in this field. Particularly, the biological activity of azasteroids has been the subject of some reviews [1–3].

The majority of medicinally useful azasteroids are synthetic compounds. Until recently, structure–activity relationships of azasteroids were determined largely by empirical methods. However, rational drug design is becoming now increasingly important for the selection of appropriate types of azasteroids as synthetic target molecule for specific medicinal application. For example, many compounds have been synthesized and studied for enzyme inhibition. Enzymes that normally transform steroid substrates may react irreversibly with reactive mimics of the latter. This can be exploited in the design of enzyme inhibitors that have medicinally useful properties stemming from their ability to block the biosynthesis of physiologically undesirable steroids further along the biosynthetic pathway.

This review is an update on the partial and total synthesis of azasteroids. The preceding report on this subject appeared in 1995 [4]. So, the focus of this review will be on the more recent results. It covers the literature from 1995 to 2007 since early work has already been reviewed [4–7]. Otherwise, numerous patents relative to the synthesis and the biological activity of 4-azasteroids are not included. We consider it is more judicious to report all of them in a review which will be written shortly.

Steroidal systems containing a nitrogen or several nitrogen atoms at various positions in the cyclopentanophenanthrene skeleton are classified as heterocyclic azasteroids or more generally azasteroidal systems.

This review is divided in sections according to the position of the heteroatom on the steroidal skeleton.

2. Syntheses of 3-azasteroids

Though many azasteroids have been reported, curiously and much to our surprise, 3-azasteroids have been reported only once and it was not a total synthesis [8]. Nevertheless, a steroidal pyridine-N-oxide proved to be a potent inhibitor of the enzyme 5α-reductase (5AR) which catalyzes the conversion of testosterone to the more potent androgen dihydrotestosterone [9].

An efficient synthesis of 3-azasteroids bearing a pyridine as an A ring was achieved recently by our group [10] *via* an intramolecular cycloaddition of *ortho*-quinodimethanes (Scheme 2).

We reported in 2002 the synthesis of a 3-aza-7-iodobicyclo[4.2.0]octa-l,3,5-triene **5** *via* a [2 + 2] cycloaddition of a 3,4-didehydropyridine and a ketene dialkylacetal [11]. The synthetic pathway is depicted in Scheme 1. The synthesis involved the [2+2] cycloaddition of a 3,4-didehydropyridine and a ketene dialkylacetal leading to 3-azabicyclo[4.2.0]octa-l,3,5-trien-7-one ketal **1**. Cycloaddition proceeded regioselectively. After deprotection of the ketal, 4-azabenzocyclobutenone **2** was reduced with $NaBH_4$ in ethanol to the corresponding azabenzocyclobutenol **3**. This latter was converted to the corresponding iodide **5** *via* its mesylate **4**.

This synthesis enabled us to carry out in 2005 the first total synthesis of (±)-3-aza-1,3,5(10)-trieno steroid **9** [10] (Scheme 2). The strategy developed in our laboratory involved an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes, which are generated by benzocyclobutene [12–19].

Thus, the alkylation of the activated spirolactone **6** [20] was carried out in refluxing acetone in the presence of anhydrous potassium carbonate and our 4-azabenzocyclobutenic derivative **4** [11]. A mixture of two cyclobutene diastereoisomers **7** (2.5:1) was isolated in 82% yield. With the aim to access pure steroids with natural stereochemistry, we performed a demethoxycarbonylation of **7** according to the Krapcho procedure (NaCN/DMSO [21]). Epimerization occurred and an inseparable mixture of 4-azabenzocyclobutene diastereoisomers **8** was isolated in 91% yield. Heating of **8** at 200 °C in 1,2,4-trichlorobenzene for 24 h yielded three isomeric steroids **9a**, **9b** and **9c**. Fortunately, these azasteroids were easily separated by flash chromatography on silica gel. Steroid **9a** exhibits a *cis–anti–trans* structure while the isomer 9b matches the *trans–anti–trans* ring fusion configuration found in the natural products. Isomer **9c** presents a *trans–anti–cis* structure.

It has been reported that a steroidal N-oxido-3-aza-1,3,5(10)-triene proved to be a good inhibitor of the enzyme 5α-reductase [9]. Oxidation of our major steroid was viewed. The pyridine nitrogen of azasteroid **9a** was oxidized with 3-chloroperbenzoic acid [22] in dichloromethane to produce the target N-oxide **10**, in good yield.

Furthermore, we proceeded to the functionalization of the terminal chain of the N-oxide steroid **10** by a Wacker-type oxidation [23]. The introduction of an acetyl group at the C17 position was then observed using palladium acetate/benzoquinone in the presence of perchloric acid [24]. The expected corresponding ketone **11** was isolated in 65% yield accompanied with minor amount of terminal aldehyde **12** resulting from an anti-Markovnikov hydroxypalladation [25].