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Facile synthesis of 11-carboxamido-androst-4,9(11)-dienes via palladium-catalyzed aminocarbonylation

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ARTICLE INFO

Article history:
Received 23 January 2007
Received in revised form
26 March 2007
Accepted 17 April 2007
Published on line 7 May 2007

Keywords:
Iodo-alkene
Carboxamide
Androstane
Palladium catalyst
Carbonylation

ABSTRACT

11-Carboxamido-androst-4,9(11)-dienes were synthesized from the corresponding 11-iodo-androst-4,9(11)-diene derivative in palladium-catalyzed aminocarbonylation reaction under mild reaction conditions. The synthesis of the iodo-alkene substrate is based on the transformation of the 11-keto derivative to hydrazone, which was treated with iodine in the presence of a base (1,1,3,3-tetramethyl guanidine). The 11-carboxamides were synthesized in moderate to high isolated yields by using simple alkyl/arylamines or amino acid methylesters as N-nucleophiles. The highly active palladium catalysts enable the homogeneous catalytic functionalization at one of the most hindered position (C-11) of the steroidal skeleton.

1. Introduction

The homogeneous catalytic reactions are widely used both for the synthesis of simple building blocks and for the functionalization of various skeletons, among them biologically important ones [1–3]. Due to their catalytic activity, chemo-, regio-, and stereoselectivity homogeneous catalysis is a steadily improving efficient method for the synthesis of new derivatives, among them steroids. There is an increasing interest in developing new strategies to introduce functional groups into specific positions of the steroidal nuclei in order to modify their biological properties. During the past two decades transition metal catalyzed reactions proved to be versatile tools both for the construction of the steroid framework from easily available building blocks and for the functionalization of the steroidal skeleton [4].

The introduction of ester and carboxamide functionalities at the A- and D-ring at the distinguished position-3 and 17, respectively [5–11], proved to be efficient moieties to tune their pharmacological activity. The 'preformed' and *in situ* palladium-catalysts have been found as highly active and selective catalysts. The functionalization of the A-and D-ring of the steroidal skeleton is straightforward also in further homogeneous catalytic reactions such as cross-coupling, dihydroxylation, and hydroformylation [4]. The chemo- and stereoselective hydrogenation of carbon–carbon double bonds in the A-ring (Δ^1, Δ^2, Δ^4), in the B-ring (Δ^5) and in the D-ring (Δ^{16}) have been carried out already in the sixties, when the novel rhodium and iridium catalysts were tested even in biologically important models [4]. However, to the best of our knowledge, no examples for the carbonylation reactions or any other carbon–carbon bond forming reactions

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doi:10.1016/j.steroids.2007.04.004

at the sterically most hindered position C-11 of the C-ring are known. Some similar functionalizations at the position C-12 of the spirostenes have been published quite recently [12].

In the present paper, we report on the efficient synthesis of steroids possessing 11-carboxamido-9(11)-ene moiety in palladium-catalyzed carbonylation of an 'iodo-vinyl' substrate bearing 11-iodo-9(11)-ene functionality. The application of the easily accessible iodo-alkenes as substrates from the corresponding ketone provides an approach for the synthesis of novel 11-functionalised steroids of potential practical importance.

2. Experimental

PPh_3, 1,1,3,3-tetramethylguanidine (TMG) and adrenosterone (**1**) were purchased from Aldrich. Commercial Et_3N, primary and secondary amines including amino acid esters (Aldrich) were used without further purification. Toluene and DMF were dried according to standard procedures.

The steroidal 11-iodo-4,9(11)-diene substrate (**4**) was synthesized in a three-step synthesis according to modified conventional synthetic procedures [13–16] by using 3,11,17-triketo derivative (**1**) as starting material. Owing to differences to the previously published methods, a detailed description of the synthesis will be given below.

The ^1H and ^{13}C NMR spectra were recorded on a VARIAN INOVA 400 spectrometer at 400 and 100.58 MHz, respectively. The chemical shifts are given as δ values (ppm) and referenced to tetramethylsilane. TLC analyses were carried out by using Merck TLC sheets (Silica gel 60 F_{254}) and chloroform, chloroform/ethanol (19/1 and 49/1), and ethyl acetate/methanol (96/4) as appropriate eluents. Mass-spectrometry data have been obtained by using a GC–MS system consisting of a Perkin-Elmer AutoSystem XL gas-chromatograph and Perkin-Elmer TurboMass mass spectrometer.

2.1. *Synthesis of 11-iodo-androst-4,9(11)-diene (4)*

2.1.1. *Reduction of 3- and 17-keto functionalities of androst-4-ene-3,11,17-trione (1)*

A mixture of adrenosterone (**1**) (4 g, 13.3 mmol), hydrazine hydrate (98%, 7.55 g, 0.15 mol), potassium hydroxide (4.64 g, 82.9 mmol), water (4.70 g) in triethylene glycol (60 ml) was heated under reflux for 45 min. The open flask was heated until the temperature of the reaction mixture reached 200 °C, then refluxing was continued for further 2 h. The solution was cooled, water was added (150 ml), neutralized by cc. HCl, extracted with ether and dried over sodium sulfate. The oily residue was purified by column chromatography (silicagel, chloroform) resulting in androst-4-en-11-one (**2**). Yield: 1.4 g; 39%.

2.1.2. *Synthesis of the 11-iodo-androst-4,9(11)-diene (4) via the corresponding hydrazone (3)*

Androst-4-en-11-one (**2**) (3.50 g, 12.9 mmol), freshly distilled hydrazine hydrate (98%, 55.47 g, 1.11 mol) and barium oxide (60 mg) in 2-methoxy-ethanol (100 ml) were heated for 4 days at 160 °C. After completion of the reaction the mixture was poured onto water and extracted with dichloromethane. Then the organic phase was dried over sodium sulfate, and evaporated to give the 11-hydrazone derivative (**3**). The product was used in the next step without further purification.

To a stirred solution of iodine (6.43 g, 25.3 mmol) in ether (70 ml) 1,1,3,3-tetramethylguanidin (TMG, 12.54 g, 108.9 mmol) was added slowly and cooled by iced water bath during the addition. The solution of **3** (3.45 g, 12.1 mmol) in ether (20 ml) was added dropwise at room temperature. After the addition was completed, the mixture was stirred for an hour. Then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 h. The mixture was poured onto water and extracted with ether. The combined organic layer was washed with 1N aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried on sodium sulfate and evaporated. Purification by column chromatography (silicagel, hexane) gave pure **4** as a yellow viscous material. Yield: 2.4 g; 52%.

2.2. *Synthesis of the 3,11,17-triiodo-androst-3,5,9(11),16-tetraene (14) via the corresponding hydrazone (13)*

Androst-4-en-3,11,17-trione (**1**) (5 g, 16.6 mmol), freshly distilled hydrazine hydrate (98%, 49.92 g, 998.4 mmol) and barium oxide (200 mg) in 2-methoxy-ethanol (50 ml) were heated for 6 days at 160 °C. After completion of the reaction the mixture was poured onto water and extracted with dichloromethane. Then the organic phase was dried over sodium sulfate, and evaporated to give the 3,11,17-tris-hydrazone derivative (**13**). The product was used in the next step without further purification.

To a stirred solution of iodine (24.47 g, 96.4 mmol) in dichloromethane (100 ml) solution of **13** (5 g, 14.6 mmol) and 1,1,3,3-tetramethylguanidin (TMG, 15.13 g, 131.4 mmol) in dichloromethane (20 ml) was added dropwise at room temperature. After the addition was completed, the mixture was stirred for an hour. Then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 3 h. The mixture was poured onto water and extracted with ether. The combined organic layer was washed with 1N aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried on sodium sulfate and evaporated. Purification by column chromatography (silicagel, hexane:EtOAc 99:1) gave pure **14** as a pale yellow solid material. Yield: 2.82 g; 27%.

2.3. *General procedure for the aminocarbonylation reaction*

A mixture of **4** (340 mg, 0.89 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol), and triphenylphosphine (13.1 mg, 0.05 mmol) were dissolved in 10 ml DMF under argon. Triethylamine (0.5 ml) and *tert*-butylamine (0.293 ml, 27 mmol) or an other N-nucleophile were added. (The alanine, glycine and proline methylester, as well as proline benzylester as N-nucleophile were used as hydrochloride salt and were measured into the reaction vessel together with the catalyst.) The atmosphere was changed to carbon monoxide (1 bar), and the reaction was conducted at 50 °C for the appropriate reaction time (see Table 1) till practically com-