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Synthesis of steroidal hydroxy esters via palladium-catalyzed carbonylation

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Abstract

A number of steroidal hydroxy esters have been synthesized by the palladium-catalyzed carbonylation of the corresponding 16,17-unsaturated substrates in the presence of diols. The reaction takes place in a highly chemo- and regioselective manner and the new compounds obtained may serve as starting materials for further functionalization of the steroidal skeleton.

Keywords: Steroid; Homogeneous catalysis; Palladium catalyst; Carbonylation

1. Introduction

Homogeneous catalytic carbonylation reactions, an easy and elegant way for carbon–carbon bond formation, serve as a powerful method in organic syntheses. Since their discovery by Reppe, much interest has been devoted to catalytic hydrocarboxylation and hydroesterification of alkynes, alkenes and dienes, and some industrially important applications have been realized [1]. Recently, efforts were made to synthesize various biologically active compounds using these reactions. Functionalization of steroid skeletons via homogeneous carbonylation found its practical application [2]. New formyl-steroids and the corresponding aminomethyl derivatives were synthesised via hydroformylation with a rhodium–phosphine catalyst prepared in situ [3]. The rhodium- and platinum-catalyzed hydroformylation of the vinylated aromatic steroids [4] and the synthesis of steroidal hydrazides via the hydrazinocarbonylation reaction [5] was also described. Palladium-catalyzed direct and carbonylative coupling reactions of various steroid derivatives possessing an iodo- or a bromo-alkenyl moiety were examined by Skoda-Földes et al. [6], as well as the direct and carbonylative vinylation of steroidal triflates [7].

In this work, catalytic hydroesterification of some androstene derivatives will be described. We have already reported the reaction of steroids with alcohols under carbonylation conditions [8]. Now we claim that monohydroxy steroidal esters can easily be prepared by reacting Δ^{16} steroids with diols in the presence of palladium

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catalyst. Similar reactions have already been carried out by Fergusson using simple olefins as starting materials [9].

2. Experimental

In a typical procedure, the solid substrate (**3**) (1.5 mmol), 0.075 mmol (52.8 mg) $PdCl_2$-$(PPh_3)_2$ and 20 mmol diol in 10 ml THF were transferred under argon to a 30 ml stainless steel autoclave equipped with a magnetic stirrer. The autoclave was pressurized to 80 bar CO and placed into an oil bath. The reaction was followed by GLC. Chromatography on silicagel with different eluents yielded the desired compounds. The isolated products were characterized by IR, MS and various NMR techniques, including 2D NMR experiments.

2.1. Instrumentation and analytical data

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity 300 (Palo Alto, CA) spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts are reported in δ ppm, referred to TMS (tetramethylsilane) as internal standard. Gas–liquid chromatographic (GLC) analyses were performed on a Shimadzu GC-14A gas chromatograph fitted with a 10 m HP-17 column. Gas chromatography-mass spectroscopy (GC-MS) measurements were carried out on a Hewlett Packard 5971A GC-MSD. Infrared (IR) spectra were recorded in KBr pellets on a Specord-IR 75 instrument.

All manipulations were performed under argon by using standard inert techniques.

(**1a**) ^1H NMR ($CDCl_3$): 0.74 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 2.96 (ddd, 1H, 16β-H); 3.59 (m, 1H, 3α-H); 3.82 (m, 2H, COOCH_2–); 4.2 (m, 2H, CH_2–CH_2–OH). ^{13}C NMR ($CDCl_3$): 12.3 (19-CH_3); 17.6 (18-CH_3); 66.0 (COOCH_2–); 61.3 (–CH_2–CH_2–OH); 178.0 (C=O). IR (KBr, ν [cm^{-1}]): 1706 (C=O). MS: 364 (M^+); 349 (M^+–CH_3); 346 (M^+–H_2O); 274; 117; 55. m.p. = 69°C. Isolated yield: 65%.

(**2a**) ^1H NMR ($CDCl_3$): 0.77 (s, 3H, 18-CH_3); 1.01 (s, 3H, 19-CH_3); 2.95 (m, 1H, 16β-H), 3.53 (m, 1H, 3α-H); 3.82 (m, 2H, COOCH_2–); 4.2 (m, 2H, CH_2–CH_2–OH); 5.35 (m, 1H, 6-H). ^{13}C NMR ($CDCl_3$): 17.4 (18-CH_3); 19.4 (19-CH_3); 66.0 (COOCH_2–); 61.3 (–CH_2–$CH2$–OH); 121.4 (6-CH); 140.7 (5-C); 178.0 (C=O). IR (KBr, ν [cm^{-1}]): 1706 (C=O). MS: 362 (M^+); 347 (M^+–CH_3); 344 (M^+–H_2O); 329; 301; 277; 55. m.p. = 53–55°C. Isolated yield: 40%.

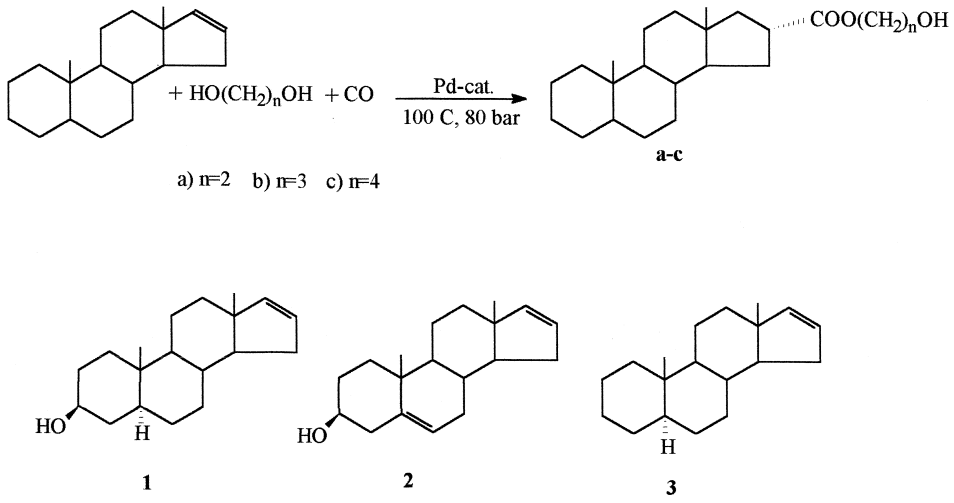
(**3a**) ^1H NMR ($CDCl_3$): 0.71 (s, 3H, 18-CH_3); 0.79 (s, 3H, 19-CH_3); 2.9 (ddd, 1H, 16β-H), 3.62 (m, 2H, COOCH_2–); 4.2 (m, 2H, CH_2–CH_2–OH). ^{13}C NMR ($CDCl_3$): 12.1 (19-CH_3); 17.6 (18-CH_3); 60.8 (COOCH_2–); 65.8 (–CH_2–CH_2–OH); 177.8 (C=O). IR (film): 1706 (CO). Yellow oil, isolated yield: 74%.

(**3b**) ^1H NMR ($CDCl_3$): 0.71 (s, 3H, 18-CH_3); 0.79 (s, 3H, 19-CH_3); 2.9 (ddd, 1H, 16β-H), 3.68 (t, 2H, COOCH_2–); 4.2 (m, 2H, CH_2–CH_2–OH). ^{13}C NMR ($CDCl_3$): 12.2 (19–CH_3); 17.7 (18-CH_3); 31.8 (–CH_2–CH_2–CH_2–); 59.2 (COOCH_2–); 61.2 (–CH_2–CH_2–OH); 178.0 (C=O). MS: 362 (M^+); 305; 286; 258; 217. Yellow oil, isolated yield: 30%.

(**3c**) ^1H NMR ($CDCl_3$): 0.71 (s, 3H, 18-CH_3); 0.79 (s, 3H, 19-CH_3); 2.9 (ddd, 1H, 16β-H), 3.68 (t, 2H, COOCH_2–); 4.2 (t, 2H, CH_2–CH_2–OH). ^{13}C NMR ($CDCl_3$): 12.2 (19-CH_3); 17.7 (18-CH_3); 29.08 (–CH_2–CH_2–CH_2–); 62.2 (COOCH_2–); 64.07 (–CH_2–CH_2–OH); 178.0 (C=O). MS: 376 (M^+); 304; 286; 243; 217. Oil, isolated yield: 30%.

3. Results and discussion

Using 5-α-androst-16-ene (**3**, Scheme 1) as a model compound, we tried to find appropriate conditions for esterification of steroids with different diols. Applying Pd(0) catalysts [$Pd(PPh_3)_4$ or $Pd(OAc)_2$ + PPh_3 forming also Pd(0) species]



Scheme 1. Hydroalkoxycarbonylation of steroids with diols.

no reaction took place, while working with the Pd(II) complex $Pd(PPh_3)_2Cl_2$, the products could be synthesized in good yields. The influence of temperature (50–150°C) and CO pressure (30–130 bar) has been investigated using **3** and ethylene glycol as model compounds (Table 1). No significant difference was noticed in the reaction rate using various CO pressures at constant temperature, while the rather slow reaction at 50°C is significantly accelerated enhancing the reaction temperature and working at constant CO pressure. Formation of diesters in THF was not detected even if an 8:1 ratio of steroid:diol was used in THF.

The chemoselectivity of esterification of **1–3** was high in all cases (Table 2), the hydrogenated product (C) was formed only in low yield (0.6–12%).

In the hydroalkoxycarbonylation of **2**, the double bond in position 5 remained intact even under severe reaction conditions probably because of steric hindrance.

The reaction of the 16,17 double bond could be carried out with high regioselectivity.

The ^1H NMR investigation of the separated products proved the 16α position of the functional group (the splitting of 16-H).

Table 1
Hydroalkoxycarbonylation of androst-16-ene at different temperatures and CO pressures

Temperature (°C)	Pressure (bar)	Conversion (%/6 h)
50	80	27
100	80	88
150	80	92
100	30	87
100	80	89
100	100	91
100	130	92

Reaction conditions: 1.5 mmol steroid; 20 mmol ethylene glycol, 0.075 mmol $PdCl_2(PPh_3)_2$, solvent: THF.

Table 2
Hydroalkoxycarbonylation of androst-16-ene derivatives with $PdCl_2(PPh_3)_2$ as catalyst

Steriod	Diol	Conversion (%/6 h)	Product distribution (%)[a]		
			A	B	C
1	$HO(CH_2)_2$ OH	98	92.7*	6.7	0.6
1	$HO(CH_2)_3$ OH	92	84.9	2.8	12.2
1	$HO(CH_2)_4$ OH	95	85.1	2.7	12.2
2	$HO(CH_2)_2$ OH	98	92.7*	6.2	1.1
2	$HO(CH_2)_3$ OH	93	94.9	3.5	1.6
2	$HO(CH_2)_4$ OH	91	94.7	2.7	2.5
3	$HO(CH_2)_2$ OH	89	91.1*	5.2	3.6
3	$HO(CH_2)_3$ OH	90	92.5*	3.9	3.5
3	$HO(CH_2)_4$ OH	89	91.7*	4.6	3.7

Reaction conditions: 1.5 mmol steroid; 20 mmol diol, 0.075 mmol $PdCl_2(PPh_3)_2$; solvent: THF; pCO = 80 bar; T = 120°C; r. time = 6 h.

[a] Determined by GLC, A: 16 α-isomer; B: 16 β-isomer; C: hydrogenated product.

* Prepared, and its structure determined by NMR.

The same stereochemistry was also revealed by different NMR techniques: DEPT, HETCOR and ^{1}H $\{^{1}H\}$ NOE methods. Using **1a** as model compound irradiation at 18-Me (0.74 ppm) resulted in an increase of the H-16 proton signal, in the opposite case, i.e., irradiation at 2.96 ppm caused an increase at the 18-Me protons. These facts prove the H-16β position, consequently, the functional group must be located in the 16α position. Its preference has been justified also energetically investigating the corresponding 16(17)-carboxy-5α, 14α-androstane by Gémes-Pécsi [10].

The minor 16β isomer (B) and the hydrogenated product (C) has been identified by GC-MS.

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