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Hydroalkoxycarbonylation of Androstene Derivatives

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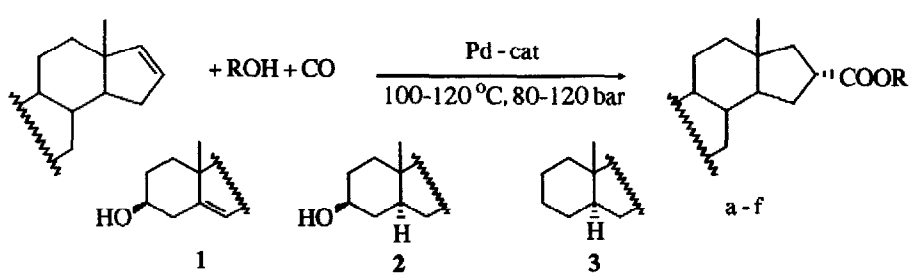
Abstract: Various esters are conveniently prepared by direct hydroesterification of the corresponding androstene derivatives with alcohols and carbon monoxide catalyzed by a palladium-phosphine catalyst with high stereoselectivity.

Introduction of alkoxycarbonyl groups into steroids via catalytic carbonylation has been investigated since years[1]. Earlier only one steroid-ester of this type has been synthesized in a multi-step reaction of low chemical yield[2].

In this paper hydroalkoxycarbonylation of several androstene derivatives with high stereoselectivity is outlined (Scheme 1). Some representative results of our systematic investigation are summarized in Table 1. The substrates (1-3) were prepared from dehydroepiandrosterone, epiandrosterone and 5α-androstan-17-one by the vinyl iodide route[3].



a) R=Me, b) R=Et, c) R=n-Pr, d) R=i-Pr, e) R=t-Bu, f) R=n-Am

Scheme 1

The reaction products were investigated by GC and 4 isomers were found but after fractional crystallization only the major compound was detected by NMR-spectroscopy.

In the hydroalkoxicarbonylation of (1) the double bond in position 5 remains intact even under more severe reaction conditions because of the steric hindrance. The reaction of Δ^{16} was carried out with high chemo- and regioselectivity. In a tipical experiment the solid substrate (1) (20 mmol), 0.25 mmol $PdCl_2(PPh_3)_2$ and 150 ml methanol were transferred under carbon monoxide to a 300 ml stainless steel autoclave equipped with a magnetic stirrer. The autoclave was pressurized to 120 bar CO pressure and placed in

an oil bath.The reaction product was prepared by fractional crystallization in 83 % yield, and its structure was based on MS, IR and NMR data.

Table 1. Hydroalkoxycarbonylation of Androst-16-ene Derivatives with the $Pd(PPh_3)_2Cl_2$ Catalyst

Steroid	Alcohol	P_{CO}, bar	Temp., °C	Conversion, %/6h	Ratio of ester isomers, % [a] A	B	C	D
1	MeOH	80	100	99	<1	94*	4	1
1	EtOH	120	120	100	7	90	2	1
2	MeOH	120	120	100	7	83*	2	8
2	EtOH	120	120	98	9	80*	6	5
2	i-PrOH	80	100	94	13	69	14	4
2	t-BuOH	80	100	80	15	80	3	2
3	MeOH	120	120	100	10	85*	4	1

[a] determined by GLC * prepared and its structure determined by NMR

In the ^{1}H-NMR investigation of the separated **2a** product the splitting of 16-H proved the 16-α position of the functional group (^{1}H-NMR: Varian XLAA-400 MHz ($CDCl_3$): 0.74 (s, 3H, 18-CH_3), 0.81 (s, 3H, 19-CH_3), 2.91 (m, $^3J_{16\beta,17b}$ ~9.0, $^3J_{16\beta,17\alpha}$ ~11.2, $^3J_{16\beta,15\alpha}$ ~2.9, $^3J_{16\beta,15\beta}$ ~9.0, 1H, 16β-H), 3.59 (m, 1H, 3α-H); ^{13}C-NMR: 101 MHz ($CDCl_3$): 12.3 (19-CH_3), 17.7 (18-CH_3), 51.7 (-OCH_3), 178.1 (-CO-)).

The same stereochemistry of the compound was supported also by its m.p. 117-118 °C and $[\alpha]_D^{20}$ = +13.4 ° (c=2.5 in $CHCl_3$) value corresponding to the data reported by Fajkos[2].
MS: m/e (rel. intensity): 334 (1000) M^+, 319 (110) M^+-CH_3, 316 (210) M^+-H_2O, 301 (190) M^+-OCH_3; IR: ν_{CO} = 1723 cm^{-1}.

The spectroscopic data of the new derivative **1a**, first synthesized by us: ^{1}H-NMR: Varian VXR-300 MHz ($CDCl_3$): 0.77 (s, 3H, 18-CH_3), 1.01 (s, 3H, 19-CH_3), 3.67 (s, 3H, -OCH_3), 2.95 (m, $^3J_{16\beta,17\beta}$ ~9.2, $^3J_{16\beta,17\alpha}$ ~11.8, $^3J_{16\beta,15\alpha}$ ~3.0, $^3J_{16\beta,15\beta}$ ~9.2, 1H, 16β-H), 3.53 (m, 1H, 3α-H), 5.35 (m, 1H, 6-H); ^{13}C-NMR: 75 MHz ($CDCl_3$): 17.4 (18-CH_3), 19.4 (19-CH_3), 51.7 (-OCH_3), 121.4 (6-CH), 140.7 (5-C), 178.1 (-CO-); MS: m/e (rel. intensity) = 332 (680) M^+, 317 (340) M^+-CH_3, 314 (970) M^+-H_2O, 299 (1000) M^+-OCH_3; IR: ν_{CO} = 1724 cm^{-1}; m.p. 54-55 °C.

The 2.95 ppm proton signal of **1a** can be assigned to H-16. The minor positiv shift (1 ppm) of C-13 and the C-14 negativ shift (-1.2 ppm) compared to the corresponding signals in 3β-OH-androstane supports the 16α location of the substituent[4]. The same stereochemistry was also proved by NOE measurements. While irradiation at 18-Me (0.77 ppm) resulted in an increase of the H-16 proton signal, in the opposite case i.e. irradiation at 2.95 ppm caused an increase at the 18-Me protons. Both facts prove the H-16β position, consequently the -$COOCH_3$ group must be located in the 16α position.

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