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Homogeneous catalytic hydroaminomethylation of steroids with aminoalcohols

Emese Nagy [a], Bálint Heil [b], Szilárd Tőrös [b,*]

[a] *Research Group for Petrochemistry of the Hungarian Academy of Sciences, H-8201 Veszprém PO Box 158, Hungary*
[b] *University of Veszprém, Department of Organic Chemistry, H-8201 Veszprém PO Box 158, Hungary*

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Dedicated to: Professor László Markó on the occasion of his 70th birthday in recognition of his outstanding contribution to organometallic chemistry.

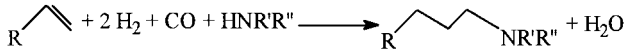
Abstract

Rhodium-catalyzed carbonylation of several Δ^{16} steroids was carried out in the presence of aminoalcohols and new hydroxy-aminomethyl derivatives have been obtained in moderate to good yields. The multi-step reaction is highly chemo- and regioselective. The new compounds containing the hydroxy function can serve as starting materials for further functionalization of the steroid skeleton. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Steroid; Homogeneous catalysis; Hydroformylation–aminomethylation; Rhodium catalyst

1. Introduction

As early as 1949, Reppe discovered [1] that aminomethylation offers a general one-pot process for the synthesis of amines from olefins and primary or secondary amines.



The reaction pathways can be formally divided into three steps: first hydroformylation of the alkene occurs followed by condensation of the aldehyde formed with the amine used and finally, subsequent hydrogenation of the imine or enamine intermediate results in the product.

The reaction catalyzed by iron pentacarbonyl was limited to ethylene and propene and required large quantities of the catalyst in a long reaction. Later, further acyclic and cyclic alkenes were also transformed [2]. The international interest in this field is obvious from the patent literature [3–5]. Laine and coworkers enhanced the catalytic activity of the system using a variety of Group 8 transition metal carbonyl precursors including the mixed ruthenium–iron catalyst [6]. Japanese authors successfully applied the $Co_2(CO)_8$-1,2bis(diphenylphosphino)ethane system in aminomethylation of propene with morpholine or piperidine as amines [7]. The isomer distribution of the reaction product was similar to that for hydroformylation of the same substrate with Co catalysts. In our laboratory rhodium catalysts prepared in situ from $[\{Rh(diene)Cl\}_2]$ and tertiary phosphines were proved to be efficient not only in hydroformylation of unsaturated Δ^{16} steroids [8] but also in aminomethylation of these derivatives [9], producing steroidal compounds previously synthesised only in a multi-step classical syntheses [10]. Kalck reported that the $[Rh_2(\mu\text{-}S\text{-}^tBu)_2(CO)_2(PPh_3)_2]$ complex catalyses the aminomethylation of terminal alkenes under low pressure of carbon monoxide and hydrogen [11]. He pointed out that the nature of the solvent has a strong influence on the course of the reaction. In THF, 98% of 1-octene was

* Corresponding author. Tel.: +36-88-422-022; fax: +36-88-427-492.
E-mail address: toros@almos.vein.hu (S. Tőrös)

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converted with diethylamine and the aminomethyl compound was produced in 80% yield with 98% selectivity of the linear derivative. A two-step route towards primary amines was recently presented by Knifton [12]. Ruthenium-catalyzed aminomethylation was reported to be highly chemo- and regioselective [13].

Aminomethylation has been extended to produce tertiary polyamines as well [14]. The polymers can be obtained by condensation of olefines with secondary polyamines or by the reaction of polyalkenes with primary or secondary amines.

In our latest efforts, carbonylation of several Δ^{16} steroids was carried out with the rhodium system in presence of aminoalcohols and new hydroxy-aminomethyl derivatives were synthesised in good yields. Some of these results will be described in the present paper.

2. Results and discussion

Our aim was to study the aminomethylation reaction of some androstene and pregnene derivatives with the rhodium catalyst described using hydroxyalkyl-amines instead of amines. Applying 3β-hydroxy-5α-androst-16-ene (**1**) as the model compound (Scheme 1) we carried out the reaction with 2-(methylamino)-ethanol in the presence of an $Rh–PBu_3$ catalyst prepared in situ, under hydroformylation conditions. As shown in Table 1, Scheme 2, high conversion was achieved and 78.4% of 3β-hydroxy-16α(β)-[*N*,*N*-(methyl, 2-hydroxy-ethylamino)methyl]-5α-androstane (see Section 3.2.4, product (d)) was obtained. The reaction of the 16, 17 double bond was highly chemoselective; no by-products were detected.

The structure of the product (d) formed was determined by NMR ($^1H–^1H$ COSY, HETCOR, NOE) measurements after isolation. The presence of a hydroxy-aminomethyl moiety in position 17 would result in coupling of the 17-H proton both with $\underline{CH_2}–N–$ (2.2–2.4 ppm) protons and with the equatorial (α) and axial (β) protons of 16-C (see Scheme 3). Thus, in the COSY spectrum a maximum of three cross-peaks is expected. Conversely, with the functional group on the 16-C, in addition to the coupling with $\underline{CH_2}–N–$ protons, the 16-H gives further cross-peaks with the 17-(α,β)H protons as well as with the 15-(α,β)H protons (max. five cross-peaks). In the COSY spectrum registered four cross-peaks can definitely be detected: the H coupling with $\underline{CH_2}–N–$ protons gives three further couplings (0.72; 1.28; 1.56 ppm). This fact throws light on the presence of the hydroxy-aminomethyl group in position 16; from the four possible isomers (16 and 17 α, β) only the 16-hydroxy-aminomethyl derivatives were formed, proving the high regioselectivity of the reaction.

As far as the stereoselectivity of the reaction is concerned, the α and β isomers are present in a 60/40% ratio (Table 2). This is in accordance with our earlier results in hydroformylation [8] of the same systems.

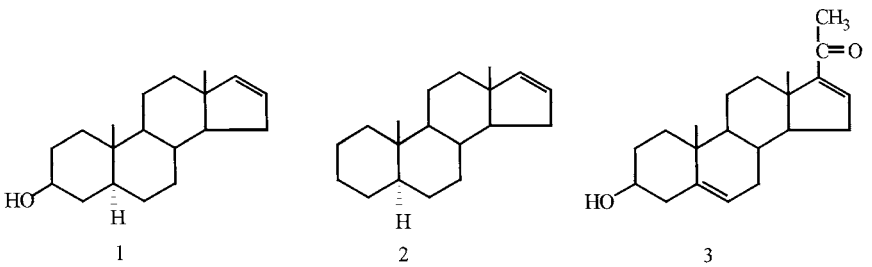
Varying the phosphine ligand of the catalytic system from the highly basic PBu_3 to the less basic PPh_3 the ratio of the 16α isomer could be enhanced. An attempt with the well-known (*S*,*S*)-DIOP reduced the hydrogenation activity of the catalyst, but the ratio of the stereoisomers was only slightly influenced.

Good yields, high chemo- and regioselectivities were achieved in hydroformylation–aminomethylation of **1** applying aminoalcohols other than 2-(methylamino)ethanol (Table 1, runs 2–5). Similar results have been obtained with **2** as substrate.

Using 3β-hydroxy-pregna-5,16-diene-20-one (**3**), the isolated product (e) turned out to be predominantly 16α ($>95\%$) according to the NMR measurements. The double bond in position 5 remains intact even under relatively severe reaction conditions because of steric hindrance. The presence of the substituent at C-17 in the pregnadiene **3** has a direct influence on stereoselectivity.

3. Experimental

$[\{Rh(nbd)Cl\}_2]$ (where nbd is 1,5-norbornadiene) was prepared according to the literature [15].



Scheme 1. Substrates used in our study.

Table 1
Aminomethylation of steroids in presence of aminoalcohols [a]

Run	Substrate	Aminoalcohol	Conv. (%)	Product distribution (%) [b]		
				A	B	C
1	1	$CH_3NH(CH_2)_2OH$	86	13.7	7.8	78.4
2	1	$CH_3CH_2CH(NH_2)CH_2OH$	100	7.4	0	92.6
3	1	$H_2N–C_6H_4–OH$	82	19	0	81
4	1	$H_2N(CH_2)_3OH$	96	8.2	0	91.8
5	1	$CH_3(CH_2)_2NH(CH_2)_2OH$	100	6.5	4.4	89.0
6	2	$CH_3NH(CH_2)_2OH$	83	16.6	0	83.3
7	2	$H_2N(CH_2)_3OH$	80.4	19.6	17.4	62.9
8	2	$CH_3CH_2CH(NH_2)CH_2OH$	70.2	29.8	0	70.2
9	2	$H_2N–C_6H_4–OH$	93	7.6	0	92.4
10	2	$CH_3(CH_2)_2NH(CH_2)_2OH$	86	13.7	5	81.1
11	3	$CH_3NH(CH_2)_2OH$	75	[c]	[c]	[c]

[a] Reaction conditions: 1.5 mmol steroid and 3 mmol of aminoalcohol in 10 ml benzene at 120°C and 80 atm of CO/H_2 (1:1). Reaction time: 6 h. Catalyst: 0.0375 mmol of $[\{Rh(nbd)Cl\}_2]$ + 0.15 mmol of PBu_3.
[b] Determined by GC.
[c] Not detectable by GC, isolated yield of product C: 32%.

Benzene was dried over sodium and distilled under argon. Aminoalcohols were purchased from Aldrich and distilled prior to use.

^{1}H- 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. Gas–liquid chromatographic (GLC) analyses were performed on a Shimadzu GC-14A gas chromatograph fitted with a 5 m HP-1 column. Gas chromatography–mass spectroscopy (GC-MS) measurements were made on a Hewlett–Packard 5971 A GC-MSD spectrometer.

Infrared (IR) spectra were recorded in KBr pellets on a Specord-IR 75 instrument.

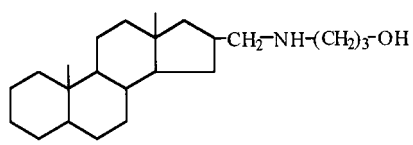
All manipulations were performed under argon using standard inert techniques.

3.1. General procedure

In a typical experiment a mixture of the steroid (1.5 mmol), $[\{Rh(nbd)Cl\}_2]$ (17.4 mg, 0.0375 mmol), the phosphine ligand (0.15 mmol) and 3 mmol of aminoalcohol in benzene (10 ml) was transferred under argon into a stainless steel autoclave. The autoclave was pressurised to 80 bar with 1:1 $CO–H_2$ and placed into an oil bath. The reaction was followed by GC. Completing the reaction, the autoclave was cooled, vented and the reaction mixture subjected to column chromatography on silica gel with different eluents (hexane, benzene, ethyl acetate, acetone, methyl alcohol). The separated and isolated products were characterised by IR, MS and various NMR techniques, including 2D NMR experiments.

3.2. Characterisation of the products

3.2.1. (a) 16α,(β)-[N-(3-Hydroxy-propylamino)-methyl]-5α-androstane



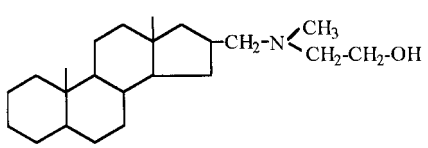
^{1}H-NMR ($CDCl_3$): 0.69 (s, 3H, 18-CH_3), 0.76 (s, 3H, 19-CH_3), 1.62 (q, 2H, NH–CH_2–CH_2), 2.86 (t, 2H, NH–CH_2–CH_2–), 3.79 (t, 2H, –CH_2–OH).

^{13}C-NMR ($CDCl_3$): 12.2 (C-19), 18.0, 20.0 (C-18), 20.62, 20.75 (C-11), 22.18 (C-2), 26.80 (C-3), 29.04 (C-6), 30.52, 30.73 (C-15), 31.85 (C-4), 32.42, 32.54 (C-7), 35.19, 35.3 (C-16), 35.73 (C-10), 36.36, 36.51 (C-8), 38.71 (C-1), 38.89, 39.49 (C-12), 40.56, 41.42 (C-13), 44.66 (C-5), 46.6, 47.0 (C-17), 50.2, 50.6 (–CH_2–OH), 53.29 (C-14), 54.83, 54.99 (C-9), 56.7, 57.2 (N–CH_2–CH_2–), 64.5 (CH_2–N).

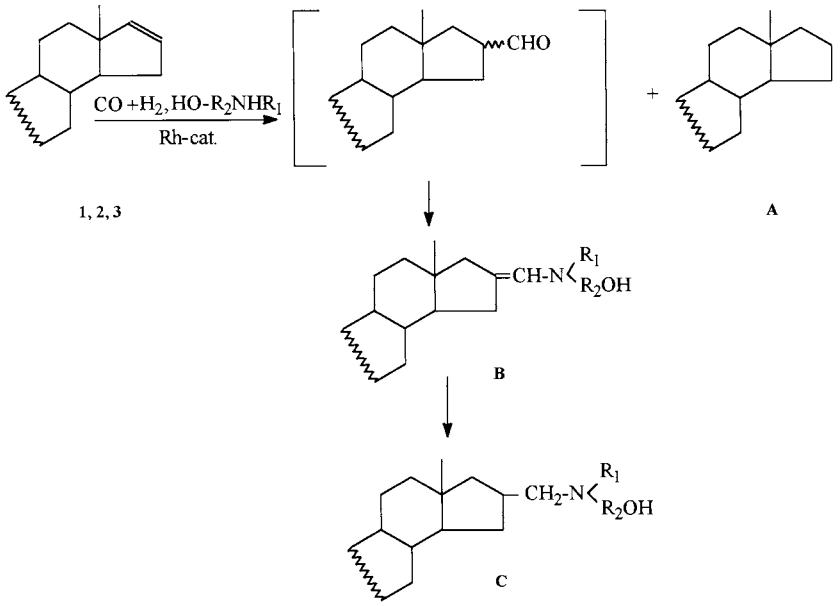
Anal. Calc. for $C_{23}H_{41}NO$ (347.31): C, 79.47; H, 11.90; N, 4.03. Found: C, 79.39; H, 12.10; N, 3.95%.

Isolated yield: 50%; m.p.: 134–137°C.

3.2.2. (b) 16α(β)-[N,N-(Methyl, 2-hydroxy-ethylamino)methyl]-5α-androstane



^{1}H-NMR ($CDCl_3$): 0.69 (s, 3H, 18-CH_3), 0.76 (s, 3H, 19-CH_3), 2.23 (s, 3H, N–CH_3), 2.50 (m, 2H, N–CH_2), 3.54 (t, 2H, –CH_2–OH).



Scheme 2. Aminomethylation reaction of steroids in presence of aminoalcohols.

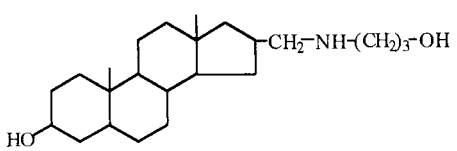
^{13}C-NMR ($CDCl_3$): 12.2 (C-19), 18.0, 20.0 (C-18), 20.64, 20.75 (C-11), 22.19 (C-2), 26.81 (C-3), 29.05 (C-6), 29.21 (C-4), 30.86, 32.25 (C-15), 32.42, 32.56 (C-7), 32.93, 34.12 (C-16), 35.31 (C-10), 35.77, 36.37 (C-8), 38.73 (C-1), 38.95, 39.52 (C-12), 40.56, 41.36 (C-13), 41.81 (N–$\underline{C}H_3$), 44.92 (C-5), 47.07 (C-17), 53.06, 54.86 (C-14), 54.91, 55.03 (C-9), 58.77 (N–$\underline{C}H_2$–CH_2–OH), 58.13 (N–CH_2–$\underline{C}H_2$–OH), 65.17 (–$\underline{C}H_2$–N).

Anal. Calc. for $C_{23}H_{41}NO$ (347.31): C, 79.47; H, 11.90; N, 4.03. Found: C, 79.10; H, 12.0; N, 3.85%.

MS (*m*/*z*, relative intensity): 316/82, 257/4, 218/4, 88/100, 41/10.

Isolated yield: 62%; m.p.: 154–157°C.

3.2.3. (c) 3β-Hydroxy-16α,(β)-[N-(3-hydroxy-propylamino)methyl]-5α-androstane



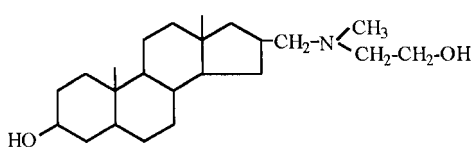
^{1}H-NMR ($CDCl_3$): 0.68 (s, 3H, 18-CH_3), 0.76 (s, 3H, 19-CH_3), 1.84 (q, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.50 (m, 2H, –NH–CH_2), 2.86 (t, 2H, $\overline{-CH_2}$–NH), 3.56 (m, 1H, 3α-H), 3.8 (t, 2H, –$\underline{CH_2}$–OH).

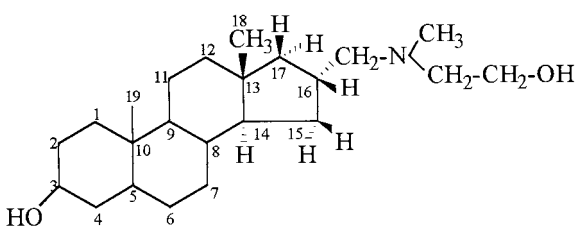
^{13}C-NMR ($CDCl_3$): $\overline{12.2}$ (C-19), 18.0, 20.0 (C-18), 21.07, 21.20 (C-11), 28.68 (C-6), 30.74 (C-2), 31.51, 31.88 (C-15), 32.32, 32.4 (C-7), 35.20, 35.25 (C-16), 35.58, 35.70 (C-8), 36.52 (C-10), 37.05 (C-4), 38.2 (C-1), 38.81, 39.41 (C-12), 40.46, 41.43 (C-13), 44.6 (–$\underline{CH_2}$–CH_2–), 44.88 (C-5), 46.6 (C-17), 50.2 ($\underline{CH_2}$–OH), $\overline{53.18}$, 54.44 (C-14), 54.59, 54.72 (C-9), $\overline{56.7}$ (NH–$\underline{CH_2}$–CH_2–), 64.5 ($\underline{CH_2}$–NH), 71.3 (C-3).

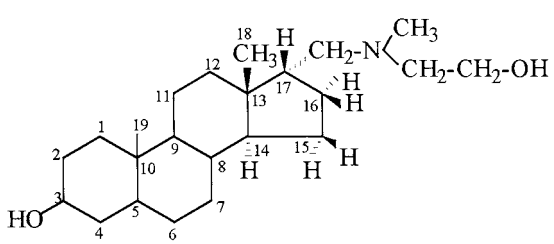
Anal. Calc. for $C_{23}H_{41}NO_2$ (363.31): C, 75.97; H, 11.37; N, 3.85. Found: C, 75.63; H, 11.55; N 3.65%.

Isolated yield: 85%; m.p.: 167–169°C.

3.2.4. (d) 3β-Hydroxy-16α(β)-[N,N-(methyl, 2-hydroxy-ethylamino)methyl]-5α-androstane







Scheme 3. Possible regioisomers of the product.

Table 2
Dependence of the 16α/16β ratio on the type of the phosphine ligand [a]

Run	Ligand	Conv. (%)	Product distribution (%)			16α/16β (%)
			A	B	C	
1	PBu_3	86	13.7	7.8	78.5	60/40
2	PPh_3	98.5	3.7	17.9	78.4	50/50
3	(*S*,*S*)-DIOP	96	9	48	43	55/45

[a] Reaction conditions: 1.5 mmol 3β-hydroxy-5α-androst-16-ene and 3 mmol of 2-(methylamino)-ethanol in 10 ml benzene at 120°C and 80 atm of H_2/CO (1:1). Reaction time: 6 h. Catalyst: 0.0375 mmol $[\{Rh(nbd)Cl\}_2]$+0.15 mmol of ligand.

^{1}H-NMR ($CDCl_3$): 0.68 (s, 3H, 18-CH_3), 0.76 (s, 3H, 19-CH_3), 3.54 (m, 1H, 3α-H), 2.23 (s, 3H, N-CH_3), 3.54 (t, 2H, –CH_2–OH), 2.52 (t, 2H, N–CH_2).

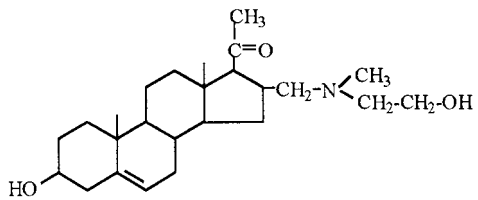
^{13}C-NMR ($CDCl_3$): 12.2 (C-19), 18.0, 20.0 (C-18), 21.04, 21.15 (C-11), 28.64 (C-6), 30.79 (C-2), 31.47, 32.18 (C-15), 32.28, 32.41 (C-7), 32.90, 34.10 (C-16), 35.23, 35.64 (C-8), 35.71 (C10), 37.00 (C-4), 38.15 (C-1), 38.82, 39.40 (C-12), 40.56, 41.36 (C-13), 41.73, 41.79 (N–$\underline{C}H_3$), 44.76 (C-5), 44.83 (N–CH_2–$\underline{C}H_2$–OH), 46.91 (C-17), 52.86, 54.39 (C-14), 54.56, 54.70 (C-9), 58.1, 58.66 (N–$\underline{C}H_2$–CH_2–OH), 65.09, 65.28 (–$\underline{C}H_2$–N), 71.22 (C-3).

Anal. Calc. for $C_{23}H_{41}NO_2$ (363.31): C, 75.97; H, 11.37; N, 3.85. Found: C, 75.55; H, 11.45; N, 3.40%.

MS (*m*/*z*, relative intensity): 332/38, 254/10, 176/13, 149/20, 88/100, 43/100, 41/52.

Isolated yield: 75%; m.p.: 119–121°C.

3.2.5. (e) 3β-Hydroxy-16α(β)-[N,N-(methyl, 2-hydroxy-ethylamino)methyl]-pregna-5-ene-20-one



^{1}H-NMR ($CDCl_3$): 0.68 (s, 3H, 18-CH_3), 0.98 (s, 3H, 19-CH_3), 2.13 (s, 3H, 21-CH_3), 2.16 (s, 3H, 25-CH_3), 2.50 (t, 2H, N–CH_2), 2.86 (m, 1H, 16-CH), 3.53 (m, 1H, 3α-H), 3.53 (t, 2H, CH_2-OH), 5.33 (d, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): 14.17 (C-18), 19.4 (C-19), 20.9 (C-16), 29.8(C-1), 31.5 (C-21), 31.6 (C-2), 31.7 (C-7), 31.9 (C-15), 35.3 (C-8), 36.5 (C-10), 37.2 (C-4), 38.9 (C-11), 41.7 (C-25), 42.2 (C-12), 44.9 (C-24), 49.9 (C-14) 55.3 (C-9), 58.4 (C-23), 59.4 (C-13), 64.8 (C-22), 70.1 (C-3), 71.6 (C-17), 121.2 (C-6), 140.7 (C-5), 208.8 (C-20).

Anal. Calc. for $C_{25}H_{41}NO_2$ (387.31): C, 77.46; H, 10.67; N, 3.62. Found: C, 77.11; H, 10.95; N, 3.25%.

MS (*m*/*z*, relative intensity): 372/55, 254/8, 169/7, 88/100, 43/85.

Isolated yield: 32%; m.p.: 197–199°C.

Acknowledgements

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