BUTTERWORTH HEINEMANN

Steroidal alkenylphosphonates via palladium-catalyzed coupling reactions

Rita Skoda-Földes, László Kollár, Judit Horváth, and Zoltán Tuba

University of Veszprém, Department of Organic Chemistry, Veszprém; Chemical Works of Gedeon Richter Ltd., Budapest, Hungary

The palladium-catalyzed coupling of various 17-iodo-Δ^{16} steroids (17-iodo-androst-16-ene, 17-iodo-4-methyl-4-aza-androst-16-en-3-one, and 17-iodo-4-aza-androst-16-en-3-one) with dialkyl phosphites (dimethyl phosphite, diethyl phosphite, and diisopropyl phosphite) was examined in detail. The only successful condition for homogeneous coupling involved carrying out the reaction in the absence of any solvents. A large excess of dialkyl phosphite was used, which means that the phosphite itself acted as a solvent. Eight new androst-16-ene derivatives with phosphonate groups at C-17 were synthesized and characterized. These steroids are of pharmacological interest as potential 5α-reductase inhibitors. Under the same conditions, methylation of lactam NH was observed using dimethyl phosphite. (*Steroids* **60**:791–795, 1995)

Keywords: coupling reaction of steroids; steroidal alkenylphosphonates; homogeneous palladium(0) catalysts

Introduction

Recognition of the importance of 5α-dihydrotestosterone (DHT) levels in many diseases has stimulated efforts to synthesize inhibitors of 5α-reductase, which is an NADPH-dependent enzyme that converts testosterone to DHT. Phosphonic acid-substituted aromatic steroids, synthesized by the hydrolysis of the corresponding phosphonates, have been shown to be efficient inactivators of this enzyme.[1]

The Michaelis-Arbuzov reaction is a well-known method for the formation of carbon-phosphorus bonds but is not applicable for the synthesis of arylphosphonates and hardly applicable for that of vinylphosphonates.[2] One of the methods used for the synthesis of these compounds is the direct reaction of vinyl- bromides with trialkyl phosphites in the presence of nickel halides. However, this method requires severe reaction conditions, and the stereochemistry of vinylphosphonates has not been clarified.[3] Other methods involve the reaction of alkenes with PCl_5, followed by esterification with ethanol and dehydrohalogenation.[4] The easiest and most elegant route for the synthesis of simple arylphosphonates and vinylphosphonates is reacting the organic bromide or iodide with dialkyl phosphite in the presence of an amine and a homogeneous Pd(0)-catalyst.[5,6] In the case of steroidal substrates, estratriene-[1] and cholesta-3,5-diene-3-phosphonate derivatives[7] were synthesized using the corresponding triflates as starting material.

In this paper, we describe the palladium-catalyzed coupling reaction of 17-iodo-androsta-16-enes (17-iodo-androst-16-ene, **1**; 17-iodo-4-methyl-4-aza-androst-16-en-3-one, **5**; 17-iodo-4-aza-androst-16-en-3-one, **9**) and dialkyl phosphites in the presence of palladium catalysts and triethylamine, which yields the corresponding Δ^{16}-17-phosphonates.

Experimental

$Pd(PPh_3)_4$ and $Pd_2(dba)_3 \cdot CHCl_3$ (where dba is dibenzylideneacetone) were prepared as described previously.[8,9] Solvents were dried (dimethylformamide over molecular sieves, toluene over sodium, acetonitrile over P_2O_5) and distilled under argon. Dialkyl phosphites were used after distillation.

The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard on a Varian Unity 300 spectrometer at 300 and 75.4 MHz, respectively. Gas-liquid chromatography (GLC) analyses were carried out on a Shimadzu GC-14A gas chromatograph fitted with a 10 m HP-17 column. Gas chromatography-mass spectroscopy (GC-MS) measurements were made on a Hewlett Packard 5971A GC-MSD; mass spectra of solid samples (**6b, 6c, 10b, 10c**) were recorded on a VG-16F mass spectrometer. Infrared spectra were recorded in KBr pellets on a Specord-IR 75 instrument.

General method for the coupling reaction of dialkyl phosphites with various steroids

In a typical experiment, 1 mmol of the steroid (**1, 5, 9**) was reacted with 25 mmol dialkyl phosphite in the presence of 0.05 mmol

Address reprint requests to László Kollár, University of Veszprém, Department of Organic Chemistry, H-8200 Veszprém, Egyetem u. 8. (P.O. Box 158) Hungary.
Received January 25, 1995; accepted July 5, 1995.

Steroids 60:791–795, 1995

655 Avenue of the Americas, New York, NY 10010

0039-128X/95/$10.00
SSDI 0039-128X(95)00121-6

$Pd_2(dba)_3 \cdot CHCl_3$ and 3 mmol Et_3N under an Ar atmosphere at 110°C for 20 h. (The reaction was monitored by GC, temperature program: initial temperature: 150°C (2 min), rate: 10°C/min, final temperature: 300°C.) Subsequently, the phosphite was removed in vacuum, and the oily product was washed with four 10 mL portions of diethyl ether. After removing the ether in vacuum, the product was purified by column chromatography on silica gel with $CHCl_3$/MeOH (95:5 v/v) as the eluent. The products were characterized by ^1H NMR, ^{13}C NMR, mass spectroscopy (MS), elemental analysis, and IR measurements.

Characterization of thef products

Dimethyl androst-16-en-17-phosphonate (*2a*). ^1H NMR (δ, $CDCl_3$): 6.65 (m, 1 H, 16-H); 3.66 (d, J = 2.4 Hz, 3 H, P-O-CH_3); 3.62 (d, J = 2.4 Hz, 3 H, P-O-CH_3); 1.0–2.3 (m, 22 H, ring protons); 0.85 (s, 3 H, 19-H_3); 0.75 (s, 3 H, 18-H_3). MS (m/z, relative intensity): 366/3 (M^+); 351/65; 281/5; 257/45; 256/100. IR: 1580 cm^{-1} (ν C = C); 1240 cm^{-1} (ν P = O); 1030 cm^{-1} (ν P-OMe). Analysis calculated for $C_{21}H_{35}PO_3$ (366.48): C 68.83; H 9.63; Found: C 68.56, H 9.81. Yield: 30%.

Diethyl androst-16-en-17-phosphonate (*2b*). ^1H NMR (δ, $CDCl_3$): 6.65 (m, 1 H, 16-H); 4.05 (m, 4 H, P-(O-CH_2-CH_3)$_2$); 2.25 (m, 1 H, 15α-H); 2.0 (m, 2 H); 1.0–1.8 (m, 19 H, ring protons); 1.32 (t, J = 6 Hz, 6 H, P-(O-CH_2-CH_3)$_2$); 0.87 (s, 3 H, 19-H_3); 0.78 (s, 3 H, 18-H_3). ^{13}C NMR (δ, $CDCl_3$): 147.2 (d, J = 14.7 Hz, 16-C); 144.0 (d, J = 182.6 Hz, 17-C); 61.1 (d, J = 5.8 Hz, P-(O-CH_2-CH_3)$_2$); 57.4 (d, J = 9.8 Hz, 14-C); 54.9 (9-C); 47.9 (d, J = 11.7 Hz, 13-C); 47.0 (5-C) 38.3; 36.2; 34.9; 33.9 (8-C); 32.8 (d, J = 18.6 Hz, 15-C); 31.9; 28.8; 28.7; 26.6; 21.9; 20.4; 16.4 (19-C); 16.2 (d, J = 6.8 Hz, P-(O-CH_2-CH_3)$_2$); 12.0 (18-C). MS (m/z, relative intensity): 394/16 (M^+); 379/100; 257/41; 256/91. IR: 1580 cm^{-1} (ν C = C); 1240 cm^{-1} (ν P = O); 1030 cm^{-1} (ν P-OEt). Analysis calculated for $C_{23}H_{39}PO_3$ (394.53): C 70.02; H 9.96; Found: C 69.85, H 10.12. Yield: 86%.

Diisopropyl androst-16-en-17-phosphonate (*2c*). ^1H NMR (δ, $CDCl_3$). 6.60 (m, 1 H, 16-H); 4.70 (m, 2 H, P-(O-C*H*-(CH$_3$)$_2$)$_2$); 2.25 (m, 1 H, 15α-H); 2.0 (m, 2 H); 1.0–1.8 (m, 19 H, ring protons); 1.28 (m, 12 H, P-(O-CH-(C*H*$_3$)$_2$)$_2$); 0.92 (s, 3 H, 19-H_3); 0.80 (s, 3 H, 18-H_3). ^{13}C NMR (δ, $CDCl_3$): 145.8 (d, J = 14.6 Hz, 16-C); 145.6 (d, J = 185.5 Hz, 17-C); 69.6 (d, J = 6.9 Hz, P-(O-*C*H-(CH$_3$)$_2$)$_2$); 57.6 (d, J = 11 Hz, 14-C); 54.9 (9-C); 47.9 (d, J = 11.7 Hz, 13-C); 47.0 (5-C); 38.3; 36.3; 34.9; 33.9 (8-C); 32.6 (d, J = 18.5 Hz, 15-C); 31.9; 28.8; 28.7; 26.6; 24.05 (d, J = 4.9 Hz, P-O-CH-*C*H$_3$); 24.0 (d, J = 3.9 Hz, P-O-CH-*C*H$_3$); 23.9 (d, J = 5.8 Hz, P-O-CH-*C*H$_3$); 23.85 (d, J = 5.9 Hz, P-O-CH-*C*H$_3$); 22.0; 20.5; 16.5 (19-C); 12.0 (18-C). MS (m/z, relative intensity): 422/10 (M^+); 407/10; 380/7; 365/17; 323/62; 257/55; 256/100. IR: 1580 cm^{-1} (ν C = C); 1240 cm^{-1} (ν P = O); 970 cm^{-1} (ν P-OiPr). Analysis calculated for $C_{25}H_{43}PO_3$ (422.59): C 71.06; H 10.26; Found: C 70.86, H 10.37. Yield: 83%.

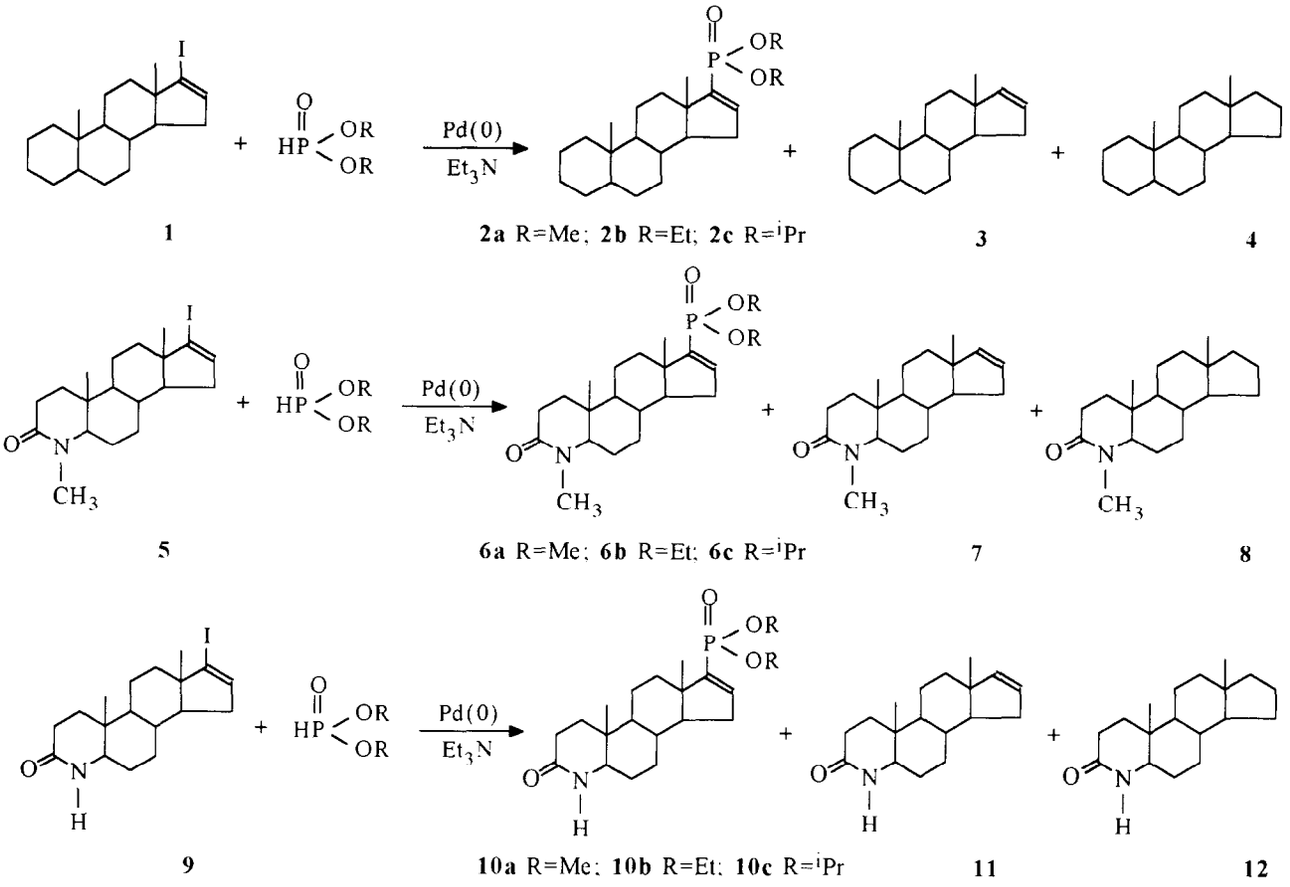
Dimethyl 4-methyl-4-aza-androst-16-en-3-on-17-phosphonate (*6a*). ^1H NMR (δ, $CDCl_3$): 6.75 (m, 1 H, 16-H); 3.78 (d, J = 2.4 Hz, 3 H, P-O-CH_3); 3.74 (d, J = 2.4 Hz, 3 H, P-O-CH_3); 3.12 (m, 1 H, 5-H); 2.93 (s, 3 H, N-CH_3); 2.50 (m, 2 H, 2-H_2); 1.4–2.4 (m, 15 H, ring protons); 0.99 (s, 3 H, 19-H_3); 0.95 (s, 3 H, 18-H_3). MS (m/z, relative intensity): 395/83 (M^+); 380/100; 286/40; 285/87; 70/57. Analysis calculated for $C_{21}H_{34}NPO_4$ (395.48): C 63.78; H 8.67; N 3.54; Found: C 63.51, H 8.79, N 3.48. Yield: 40%.

Diethyl 4-methyl-4-aza-androst-16-en-3-on-17-phosphonate (*6b*). ^1H NMR (δ, $CDCl_3$): 6.68 (m, 1 H, 16-H); 4.10 (m, 4 H, P-(O-CH_2-CH_3)$_2$); 3.08 (m, 1 H, 5-H); 2.93 (s, 3 H, N-CH_3); 2.45 (m, 2 H, 2-H_2); 1.4–2.4 (m, 15 H, ring protons); 1.35 (t, J = 6 Hz, 6 H, P-(O-CH_2-CH_3)$_2$); 0.95 (s, 3 H, 19-H_3); 0.92 (s, 3 H, 18-H_3). ^{13}C NMR (δ, $CDCl_3$): 170.2 (3-C); 146.6 (d, J = 14.6 Hz, 16-C); 143.8 (d, J = 183.7 Hz, 17-C); 65.3 (5-C); 61.0 (d, J = 4.9 Hz, P-(O-CH_2-CH_3)$_2$); 56.6 (d, J = 10.7 Hz, 14-C); 51.8 (9-C); 47.8 (d, J = 12.7 Hz, 13-C); 36.2 (10-C); 34.4 (2-C); 32.6 (8-C); 32.4; 32.5 (15-C); 29.8; 28.7 (N-CH_3); 28.7; 25.0; 20.6; 16.3 (19-C); 16.07 (d, J = 5.8 Hz, P-(O-CH_2-CH_3)$_2$); 12.0 (18-C). MS (m/z, relative intensity): 423/20 (M^+); 408/65; 286/40; 285/57; 163/92; 83/85; 69/52; 43/100. IR: 1630 cm^{-1} (ν NC = O); 1580 cm^{-1} (ν C = C); 1230 cm^{-1} (ν P = O); 1040 cm^{-1} (ν P-OEt). Analysis calculated for $C_{23}H_{38}NPO_4$ (423.53): C 65.23; H 9.04; N 3.31; Found: C 65.11, H 9.14, N 3.27. Yield: 91%.

Diisopropyl 4-methyl-4-aza-androst-16-en-3-on-17-phosphonate (*6c*). ^1H NMR (δ, $CDCl_3$): 6.62 (m, 1 H, 16-H); 4.70 (m, 2 H, P-(O-C*H*-(CH$_3$)$_2$)$_2$); 3.08 (m, 1 H, 5-H); 2.93 (s, 3 H, N-CH_3); 2.45 (m, 2 H, 2-H_2); 1.4–2.4 (m, 15 H, ring protons); 1.34 (d, J = 6.1 Hz, 6 H, P-O-CH-(C*H*$_3$)$_2$); 1.32 (d, J = 6.4 Hz, 3 H, P-O-CH-C*H*$_3$); 1.29 (d, J = 6.4 Hz, 3 H, P-O-CH-C*H*$_3$); 0.95 (s, 3 H, 19-H_3); 0.92 (s, 3 H, 18-H_3). ^{13}C NMR (δ, $CDCl_3$): 170.3 (3-C); 145.4 (d, J = 14.6 Hz, 16-C); 145.3 (d, J = 186.5 Hz, 17-C); 69.6 (d, J = 5.8 Hz, P-(O-*C*H- (CH$_3$)$_2$)$_2$); 65.4 (5-C); 56.7 (d, J = 9.7 Hz, 14-C); 51.9 (9-C); 47.8 (d, J = 11.8 Hz, 13-C); 36.3 (10-C); 34.5 (2-C); 32.6 (8-C); 32.4; 32.5 (d, J = 15.6 Hz, 15-C); 29.8; 28.7 (N-*C*H$_3$); 28.7; 25.0; 23.92 (d, J = 4.8 Hz, P-O-CH-*C*H$_3$); 23.87 (d, J = 4 Hz, P-O-CH-*C*H$_3$); 23.80 (d, J = 4.8 Hz, P-O-CH-*C*H$_3$); 23.74 (d, J = 4.9 Hz, P-O-CH-*C*H$_3$); 20.6; 16.4 (19-C); 12.0 (18-C). MS (m/z, relative intensity): 451/9 (M^+); 436/6; 352/60; 286/35; 285/40; 84/65; 83/100; 70/53. IR: 1630 cm^{-1} (ν NC = O); 1580 cm^{-1} (ν C = C); 1230 cm^{-1} (ν P = O); 980 cm^{-1} (ν P-OiPr). Analysis calculated for $C_{25}H_{42}NPO_4$ (451.59): C 66.49; H 9.37; N 3.10; Found: C 66.32, H 9.42, N 3.07. Yield: 89%.

Diethyl 4-aza-androst-16-en-3-on-17-phosphonate (*10b*). ^1H NMR (δ, $CDCl_3$): 6.8 (s, 1 H, NH); 6.65 (m, 1 H, 16-H); 4.10 (m, 4 H, P-(O-CH_2- CH_3)$_2$); 3.08 (m, 1 H, 5-H); 2.40 (m, 2 H, 2-H_2); 1.3–2.35 (m, 15 H, ring protons); 1.32 (t, J = 6 Hz, 6 H, P-(O-CH_2-C*H*$_3$)$_2$); 0.95 (s, 3 H, 19-H_3); 0.92 (s, 3 H, 18-H_3). ^{13}C NMR (δ, $CDCl_3$): 172.4 (3-C); 146.8 (d, J = 14.6 Hz, 16-C); 143.8 (d, J = 183.7 Hz, 17-C); 61.1 (d, J = 4.9 Hz, P-(O-CH_2-CH_3)$_2$); 60.4 (5-C); 56.7 (d, J = 9.8 Hz, 14-C); 51.3 (9-C); 47.9 (d, J = 11.7 Hz, 13-C); 35.5 (10-C); 34.5 (2-C); 33.4 (8-C); 33.0; 32.6 (d, J = 17.5 Hz, 15-C); 29.3; 28.3; 26.7; 20.7; 16.4 (19-C); 16.1 (d, J = 6.9 Hz, P-(O-CH_2-CH_3)$_2$); 11.1 (18-C). MS (m/z, relative intensity): 409/12 (M^+); 394/82; 272/54; 271/100; 85/53; 84/80. IR: 3160 cm^{-1} (ν NH); 1680 cm^{-1} (ν NC = O); 1580 cm^{-1} (ν C = C); 1230 cm^{-1} (ν P = O); 1020 cm^{-1} (ν P-OEt). Analysis calculated for $C_{22}H_{36}NPO_4$ (409.51): C 64.53; H 8.86; N 3.42; Found: C 64.35, H 8.92, N 3.35. Yield: 92%.

Diisopropyl 4-aza-androst-16-en-3-on-17-phosphonate (*10c*). ^1H NMR (δ, $CDCl_3$): 7.15 (brs, 1 H, NH); 6.60 (m, 1 H, 16-H); 4.70 (m, 2 H, P-(O- C*H*-(CH$_3$)$_2$)$_2$); 3.08 (m, 1 H, 5-H); 2.40 (m, 2 H, 2-H_2); 1.4–2.35 (m, 15 H, ring protons); 1.34 (d, J = 6.1 Hz, 6 H, P-O-CH-(C*H*$_3$)$_2$); 1.32 (d, J = 6.4 Hz, 3 H, P-O-CH-C*H*$_3$); 1.29 (d, J = 6.4 Hz, 3 H, P-O-CH-C*H*$_3$); 0.95 (s, 3 H, 19-H_3); 0.92 (s, 3 H, 18-H_3). ^{13}C NMR (δ, $CDCl_3$): 172.3 (3-C); 145.5 (d, J = 14.6 Hz, 16-C); 145.4 (d, J = 186.6 Hz, 17-C); 69.7 (d, J = 5.9 Hz, P-(O-*C*H- (CH$_3$)$_2$)$_2$); 60.5 (5-C); 56.8 (d, J = 10.7 Hz, 14-C); 51.4 (9-C); 47.9 (d, J = 12.7 Hz, 13-C); 35.6 (10-C); 34.5 (2-C); 33.5 (8-C); 33.0; 32.5 (d, J = 18.6 Hz, 15-C); 29.3; 28.3; 26.8; 24.0 (d, J = 4.9 Hz, P-O-CH-*C*H$_3$); 23.95 (d, J = 3.9 Hz, P-O-CH-*C*H$_3$); 23.87 (d, J = 4.9 Hz, P-O-CH-*C*H$_3$); 23.80 (d, J = 4.9 Hz, P-O-CH-*C*H$_3$); 20.7; 16.5 (19-C); 11.1



Scheme 1 Reaction of various steroids with dialkyl phosphites.

(18-C). MS (m/z, relative intensity): 437/2 (M^+); 422/3; 338/28; 272/20; 271/30; 84/100. IR: 3180 cm^{-1} (ν NH); 1680 cm^{-1} (ν NC = O); 1580 cm^{-1} (ν C = C); 1230 cm^{-1} (ν P = O); 980 cm^{-1} (ν P-OiPr). Analysis calculated for $C_{24}H_{40}NPO_4$ (437.50): C 65.88; H 9.21; N 3.20; Found: C 65.64, H 9.32, N 3.16. Yield: 93%.

Results and discussion

Using 17-iodo-androst-16-ene (**1**, Scheme 1) as a model compound, we tried to find appropriate conditions for coupling the steroid with diisopropyl phosphite. Applying numerous solvents (acetonitrile, toluene, dimethylformamide), amines (triethylamine, *N*-methyl-morpholine), and catalysts ($Pd(PPh_3)_4$, $Pd_2(dba)_3 \cdot CHCl_3$) generally used in such coupling reactions, yielded only traces of the desired product, even after prolonged heating (Table 1). Only the addition of an excess of dialkyl phosphite seemed to improve the conversion (Run 5), but only to a small extent.

By reacting the steroid with a high excess of dialkyl phosphite (25 Eq) in the absence of any solvents, the product could be synthesized in good yields in the presence of various Pd catalysts (Table 2). The reaction mixture was homogeneous at the applied temperature, and no catalyst-decomposition could be observed. Analysis of the mixture by GC-MS showed that, besides the desired phosphonate derivative, approximately 20% of androstane (**4**) and an-

Table 1 Reaction of 17-iodo-androsta-16-ene (**1**) with diisopropyl phosphite in the presence of triethylamine and $Pd_2(dba)_3 \cdot CHCl_3$

Run	Solvent	Amine/ substrate	Phosphite/ substrate	Substrate/Pd	Reaction time (h)	Yield (%)
1	Acetonitrile	1.5[a]	1	40[b]	9	—[c]
2	Toluene	1	1	40[b]	9	Traces
3	Toluene	3	1	40	9	Traces
4	Toluene	10	1	40	9	Traces
5	Toluene	3	10	40	9	11
6	*N*-Me-Morpholine	—	2	40	9	—[c]
7	Triethylamine	—	2	40	9	—[c]
8	Dimethylformamide	3	10	40	9	Traces

[a] *N*-Me-Morpholine was used as the amine component; reaction temperature 70°C.
[b] $Pd(PPh_3)_4$ was used as a catalyst.
[c] No reaction.

Table 2 Reaction of 17-iodo-androst-16-ene (**1**) with diisopropyl phosphite using the phosphite as solvent

Run	Catalyst	Et_3N/ substrate	Substrate/Pd	Reaction time (h)	Conversion (%)[a]	Product distribution[b] (%)	
						2c	**3 + 4**
1	$Pd_2(dba)_3 \cdot CHCl_3$	1	40	9 (24)	74 (>99)	78	22
2	$Pd_2(dba)_3 \cdot CHCl_3$	3	40	4 (9)	81 (>99)	80	20
3	$Pd_2(dba)_3 \cdot CHCl_3$	10	40	2 (4)	83 (>99)	87	13
4	$Pd_2(dba)_3 \cdot CHCl_3$	3	100	9	63	74	26
5	$Pd_2(dba)_3 \cdot CHCl_3$	10	100	9 (24)	82 (>99)	82	18
6	$Pd(PPh_3)_4$	3	40	9 (24)	23 (35)	75	25
7	$Pd_2(dba)_3 \cdot CHCl_3 + 4\ PPh_3$	3	40	4 (9)	84 (86)	82	18
8	$Pd(OAc)_2$	3	40	9 (24)	58 (75)	93	7
9	$Pd(OAc)_2 + 2PPh_3$	3	40	4 (9)	67 (77)	81	19

[a]Mol reacted substrate/mol initial substrate × 100.
[b]Mol product/mol reacted substrate × 100.

drostene isomers (**3**) produced possessed unsaturation in ring D (Scheme 1). Hydrodehalogenation as a side reaction was observed by other authors,[10] but the mechanism has not been clarified. Running the reaction without a catalyst demonstrated that hydrodehalogenation takes place to some extent even in the absence of catalyst. Reduction of organic bromides with diethyl phosphite and triethylamine has been reported,[11] but in this case only activated halogen atoms were reactive towards reduction. The reduction of 17-iodo-Δ^{16} derivatives may be accelerated by a hydrido-palladium species formed by the oxidative addition of dialkyl phosphite to palladium(0)-complex.

The formation of the products can be explained by the following mechanism: The palladium(0) species undergoes oxidative addition with alkenyl iodide to give the alkenylpalladium complex. The attack of dialkyl phosphite on this complex leads to the dialkyl alkenylphosphonate. Triethylamine regenerates palladium(0) with the deposition of $Et_3N \cdot HI$. The palladium(0) species obtained this way is available for another catalytic cycle. According to the literature, the reaction with aryl bromides also proceeds with dialkyl sodiophosphites in the place of dialkyl phosphites and produces reasonable yields.[10] This suggests that the reaction probably involves formation of an intermediate, arylpalladium dialkyl phosphonate, which reductively eliminates the arylphosphonate diester.

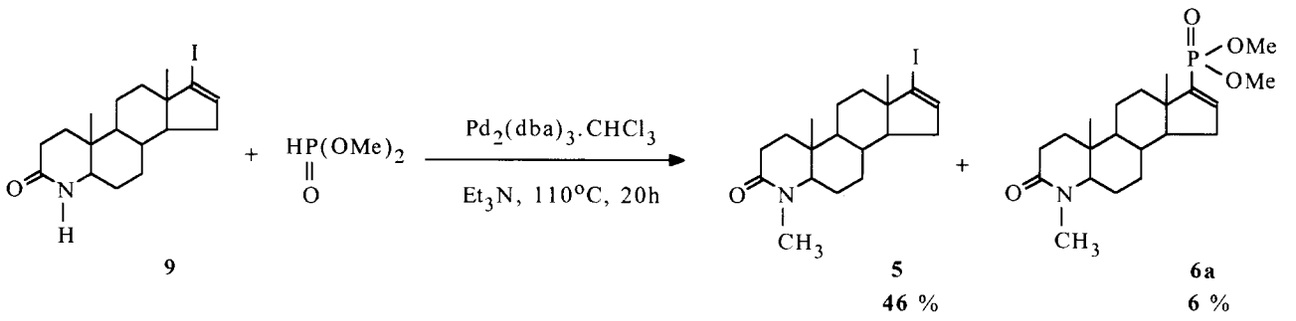
Analogously, in our case an alkenylpalladium dialkyl phosphonate intermediate may be produced. This intermediate can be formed by two routes: First, as mentioned above, by oxidative addition of the alkenyl iodide to the palladium(0) complex followed by attack of the dialkyl phosphite. Second, by reaction of the dialkyl phosphite with the palladium(0) species producing an H-Pd-P(O)$(OR)_2$ intermediate which reacts with the iodoalkenyl substrate to give the alkenylphosphonate. This H-Pd-P(O)$(OR)_2$ intermediate may also act as a simple reducing agent for the iodo-alkenyl moiety and results in a hydrodehalogenated steroid possessing a Δ^{16} double bond. This compound can isomerize producing steroids with Δ^{15} or more stable Δ^{14} double bonds. The hydrido-palladium intermediate formed during the reaction of palladium(0) with dialkyl phosphite may hydrogenate the Δ^{16}, Δ^{15}, or Δ^{14} steroids, resulting in a compound with a saturated D-ring.

The influence of reaction conditions on conversion of the substrates and on the yield of the desired product was also examined (Table 2). Increasing the amount of triethylamine greatly increased conversion due to the formation of Pd(0) complexes via HI abstraction, which is crucial for oxidative addition of the H-P bond. The chemoselectivity could also be improved to some extent (Run 1–3). Applying a greater amount of amine produced good results even if the substrate/catalyst ratio was increased, although in this case the chemoselectivity was somewhat poorer (Run 4–5). The presence of 2 PPh_3 ligands for each Pd atom in the catalyst decreased the conversion slightly, especially for reactions with longer reaction times (Runs 7 and 9). Using a catalyst with a $PPh_3/Pd = 4$ ratio considerably decreased the conversion (Run 6). Considering the product/side-product ratio, $Pd(OAc)_2$ was the best catalyst (Run 8). In this case, the conversion was relatively poor compared to that obtained with $Pd_2(dba)_3 \cdot CHCl_3$ for example (Run 2). This can be explained by the fact that when $Pd(OAc)_2$ is used as a catalyst, the first step of the reaction involves the reduction of the precursor Pd(II) complex to Pd(0), which is a well-known reaction in the presence of PPh_3.[12] In the absence of phosphine the dialkyl phosphite may serve as a reducing agent. Thus, it turned out that under the above reaction conditions, the palladium(0) precursors, which bear

Table 3 Reaction of various steroids with $HP(O)(OR)_2$ in the presence of triethylamine and $Pd_2(dba)_3 \cdot CHCl_3$ using the phosphite as solvent

Run	Substrate	R	Product	Reaction time (h)	Yield (%)[a]
1	1	Me	**1a**	22	57
2	1	Et	**1b**	4	89
3	1	iPr	**1c**	9	47
4	5	Me	**2a**	30	69
5	5	Et	**2b**	20	>90[b]
6	5	iPr	**2c**	20	>90[b]
7	9	Et	**3b**	20	>90[b]
8	9	iPr	**3c**	20	>90[b]

[a]Mol product/mol initial substrate × 100.
[b]Determined by ^1H NMR.



+ isomers of **5** and **9** : **43%**

+ hydrodehalogenated products of **5** and **9** (**7**, **11**) : **5%**

Scheme 2 Reaction of 17-iodo-4-aza-androst-16-en-3-one with $HPO(OMe)_2$.

ligands of lower basicity, were superior both to those containing phosphines and to palladium(II) complexes, which must be reduced in situ before they can act as active catalytic intermediates.

The reactivities of some dialkyl phosphites (Me, Et, iPr) were also compared (Table 3). The dimethyl derivative was found to react very slowly, giving 57% conversion after 22 h of heating. Diethyl phosphite proved to be the best of the three phosphorous compounds (Run 2). The same phenomenon was observed in the case of the other two substrates (17-iodo-4-methyl-4-aza-androst-16-en-3-one, **5** and 17-iodo-4-aza-androst-16-en-3-one, **9**) although no exact data can be given in the last four cases (Runs 5–8) because the reaction mixtures could not be analyzed by GC under the conditions used. 17-Iodo-4-aza-androst-16-en-3-one (**9**) showed special behavior upon reacting with dimethyl phosphite (Scheme 2): the formation of **5, 6a,** and isomers of **5** and **9** were detected by GC-MS instead of the desired product **10a.** These isomers have retention times completely different from those of **5** or **9,** and according to mass spectra, the isomers have molecular ions with the same weight but different fragmentation as compared to **5** and **9.** Although these isomers could not be isolated, and their correct structures were not determined, MS data suggest that opening of the A-ring resulted in the open-chain amides. This phenomenon can be explained by the presence of P(OH) derivatives formed by NH-methylation. Reducing the reaction time (5 h) produced **5, 9,** and traces of the coupling products **6a** and **10a** in the reaction mixture. Above all, dimethyl phosphite acts as a methylation agent for lactam-NH, and the methylation seems to be much faster than the expected carbon-phosphorus coupling reaction.

Acknowledgment

The authors thank the Hungarian National Science Foundation and the Commission of the European Communities for financial support (OTKA 4292 and COST PL927474).

References

1. Holt DA, Levy MA, Metcalf BW (1989; SmithKline Beckman Corporation, Philadelphia) US Patent 4,882,319.
2. Sasse K (1963). Phosphonsäuren und Derivate. In: Müller E (ed), *Houben-Weyl, Methoden der organischen Chemie*. Georg Thieme Verlag, Stuttgart, Vol. XII/1, p. 338.
3. Tavs P, Weitkamp H (1970). Preparation and NMR spectra of some α,β-unsaturated phosphonates. Nickel salt catalyzed reaction of vinyl halides with trialkyl phosphites. *Tetrahedron* **26**:5529–5534.
4. Kosolapoff GM, McCullough IF (1951). Addition reactions in phospho-organic syntheses. II. The addition of phosphorus pentachloride to normal olefins. *J Am Chem Soc* **73**:855–856.
5. Hirao T, Masunaga T, Ohshiro Y, Agawa T (1980). Stereoselective synthesis of vinylphosphonate. *Tetrahedron Lett* **21**:3595–3598.
6. Hirao T, Masunaga T, Ohshiro Y, Agawa T (1981). A novel synthesis of dialkyl arenephosphonates. *Synthesis* 56–57.
7. Holt DA, Erb JM (1989). Palladium-catalyzed phosphorylation of alkenyl triflates. *Tetrahedron Lett* **30**:5393–5396.
8. Coulson DR (1970). Tetrakis(triphenylphosphine)palladium(0). *Inorg Synth* **13**:121–124.
9. Ukai T, Kawazura H, Ishii Y (1974). Chemistry of dibenzylideneacetone-palladium(0) complexes I. Novel tris(dibenzylideneacetone)dipalladium(solvent) complexes and their reactions with quinones. *J Organomet Chem* **65**:253–266.
10. Hirao T, Masunaga T, Yamado N, Ohshiro Y, Agawa T (1982). Palladium-catalyzed new carbon-phosphorus bond formation. *Bull Chem Soc Jpn* **55**:909–913.
11. Hirao T, Kohno S, Ohshiro Y, Agawa T (1983). Reduction of organic halides with diethyl phosphonate and triethylamine. *Bull Chem Soc Jpn* **56**:1881–1882.
12. Amatore C, Jutand A, M'Barki MA (1992): Evidence of the Formation of Zerovalent Palladium from $Pd(OAc)_2$ and Triphenylphosphine. *Organometallics* **11**:3009–3013.