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Facile Synthesis of Steroidal Phenyl Ketones via Homogeneous Catalytic Carbonylation

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Abstract—Steroidal phenyl ketones were synthesised in high yields by palladium-catalysed carbonylation reactions of 17-iodo-androst-16-ene derivatives in the presence of $NaBPh_4$ under mild reaction conditions. Alkenyl bromides or enol triflates gave lower yields in the same reaction. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Until now, only a limited number of methods for the synthesis of unsymmetrical ketones under carbonylation conditions have been reported. Reaction of alkyl halides or tosylates with $Na_2[Fe(CO)_4]$ gives anionic alkyliron complexes which can react further with alkylating agents to give ketones in good yields.[1] Alkyl halides, conjugated dienes and CO react in the presence of $[Co(CO)_4]^-$ catalyst and a stoichiometric amount of base resulting in the formation of acyl dienes.[2] Carbonylation of $R_2(CN)CuLi_2$ type reagents leads to a product which can be used for the nucleophilic 1,4-acylation of α,β-unsaturated aldehydes and ketones.[3]

The palladium-catalysed three component coupling reaction between arylmetal reagents, CO and aryl halides/triflates is an attractive route for the synthesis of aryl ketones. The reagents can be organotin compounds,[4–7] arylboronic acids[8] or arylfluorosilanes.[9] Aryl iodides have been also described to react with alkyl iodides in CO atmosphere in the presence of a stoichiometric quantity of Zn/Cu and a catalytic amount of $Pd(PPh_3)_4$.[10]

We have previously reported our results concerning the palladium-catalysed carbonylation of steroidal alkenyl iodides and enol triflates in the presence of organotin reagents to give unsaturated ketones before.[11] Although $NaBPh_4$ has been used in the presence of a palladium catalyst for the arylation of enol triflates[12] or acid chlorides[13] and also, as an anion transfer agent in cascade cyclisation-anion capture processes,[14] the synthesis of phenyl ketones via carbonylation of alkenyl iodides in the presence of $NaBPh_4$ is unprecedented.

Results and Discussion

17-Iodo-androst-16-ene **1** was reacted with atmospheric CO and $NaBPh_4$ in the presence of palladium(II) acetate, triphenylphosphine and triethylamine in toluene (Scheme 1). Phenyl ketone **2** was isolated in good yield (84%). However, a side product (17-(*N*,*N*-diethyl-carboxamido)-androst-16-ene) was also detected in the reaction mixture by GC–MS.[†] It has been reported that amides can be obtained even when only tertiary amines are present in the carbonylation of iodoarenes.[15]

Toluene was found to be superior compared to DMF, which is usually used as solvent in coupling reactions. In the case of toluene, it is easier to achieve absolutely water-free conditions, which is essential for the completion of the desired reaction. In the presence of traces of water, the formation of a steroidal 17-carboxylic acid derivative was also observed. This side reaction is usually suppressed when

Keywords: Pd-catalysis; carbonylation; phenyl ketones; steroids.

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[†] MS data for 17-(*N*,*N*-diethyl-carboxamido)-androst-16-ene: *m/e* 357 (M^+)/72; 342/100; 285/20; 257/5; 100/23; 72/15.

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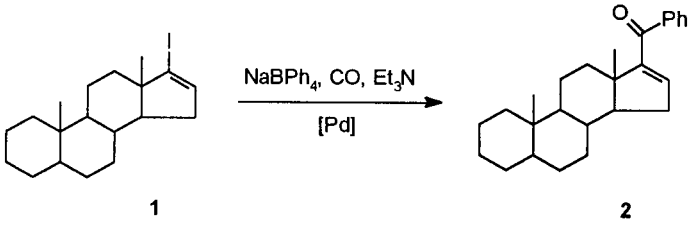

Scheme 1. Reaction of 17-iodo-androst-16-ene (**1**) with $NaBPh_4$ under carbonylation conditions.

Table 1. Carbonylation of **1** in the presence of $NaBPh_4$ (Reaction conditions: 1 mmol substrate (**1**), 0.05 mmol catalyst, $NaBPh_4$ as indicated, in 10 ml toluene under CO)

Run	$NaBPh_4$/steroid	Base	Catalyst	Reaction time [h]	Conv. [%]	Yield[a] [%]
1	1	–	$Pd(OAc)_2$+2 PPh_3	3	98	98
2	0.5	–	$Pd(OAc)_2$+2 PPh_3	12	38	38
3	0.5	Et_3N	$Pd(OAc)_2$+2 PPh_3	3	98	79
4	0.25	Et_3N	$Pd(OAc)_2$+2 PPh_3	3	>98	60
5	1	–	$Pd(PPh_3)_4$	3	98	98
6	0.5	Et_3N	$Pd(PPh_3)_4$	3	99	99
7	0.25	Et_3N	$Pd(PPh_3)_4$	3	95	95

[a] Determined by GC: (mmol ketone **2**/mmol substrate **1**)×100.

the reagents used are stronger nucleophiles (amines, hydrazine and hydroxylamine derivatives).[16,17]

As it was observed before during arylation,[12] the presence of the base was not essential for completion of the reaction when 1 equiv. of $NaBPh_4$ was used. In this case the desired product **2** was formed exclusively and it could be isolated in high yield (95%). However, when the borate/steroid ratio was 1:2 or lower, the reaction could not be completed in the absence of the base even with long reaction times. Complete conversion could be achieved in the presence of Et_3N, but the side reaction leading to the amide derivative became more pronounced resulting in a decrease in the yield of **2** (Table 1, runs 3,4).

The activity of $Pd(PPh_3)_4$ was equal to that of the $Pd(OAc)_2$+2 PPh_3 system (run 5). At the same time, the use of the $Pd(PPh_3)_4$ catalyst made it possible to decrease the borate/steroid ratio without loss of selectivity: no formation of the amide was observed (runs 6,7). That means that the excess of the phosphine ligand inhibits activation of Et_3N but it has no such effect on ketone formation.

As another advantage, this catalyst makes it possible to use all of the phenyl groups of $NaBPh_4$ (or of BPh_3 formed after the first transfer) for the production of the steroidal ketone **2**. No formation of benzophenone and biphenyl was observed, which can lower the phenyl-transfer capacity of the borate toward steroidal substrates.

17-Iodo-3-metoxy-estra-1,3,5(10),16-tetraene (**3**), 17-iodo-6α-hydroxy-3α,5α-cycloandrost-16-ene (**5**), 17-bromo-androsta-2,16-diene (**7**), 3-trifiloxy-17β-benzoyloxy-androst-2-ene (**9**), 3-trifiloxy-17β-(3′-methyl-pentan-1′,5′-diyl)carboxamido-androsta-3,5-diene (**11**) and 3-trifiloxy-estra-1,3,5(10)-trien-17-one (**13**) (Fig. 1.) were reacted under the standard reaction conditions with 1 equiv. of $NaBPh_4$.

The 17-benzoyl derivative of **3** was obtained in high isolated yield (**4**, Fig. 1, 88%). On the basis of TLC and NMR measurements the reaction is practically complete in 6 h at 90°C and no side products are formed; **6** was produced in moderate yield (55%). In the side product the 6-OH functionality of **6** was partially transformed, probably to a borate ester derivative.‡ The reactivity of **7** was found to be lower than that of the corresponding iodo-derivatives (83% conversion after 22 h, determined by GC). The enol triflates **9** and **11** did not give clean reactions and the target compounds **10** and **12** were obtained in moderate isolated yields (45 and 57%, respectively). Surprisingly, with these substrates the side reaction was direct phenylation. No such phenomenon was observed with any other substrates. No conversion could be achieved in the case of **13** even in the presence of LiCl.[18] This compound also failed to undergo the hydrazinocarbonylation reaction reported previously.[16]

Conclusion

Steroidal alkenyl iodides can be converted to the corresponding phenyl ketones, intermediates of secondary alcohols of potential practical importance under mild reaction conditions in high yields. The use of catalytic amount of $Pd(PPh_3)_4$ together with an excess of Et_3N makes it possible to use borate/steroid ratios lower than 1. Alkenyl bromides or enol triflates can also be used as substrates. One of the greatest advantages of this methodology is the tolerance towards various functional groups and therefore wide synthetic applicability.

‡ In the ^1H NMR spectrum the 6-H signal of **6** moves from 3.22 to 4.57 ppm, and one of the 4-H signals moves from 0.28 to 0.41 ppm.

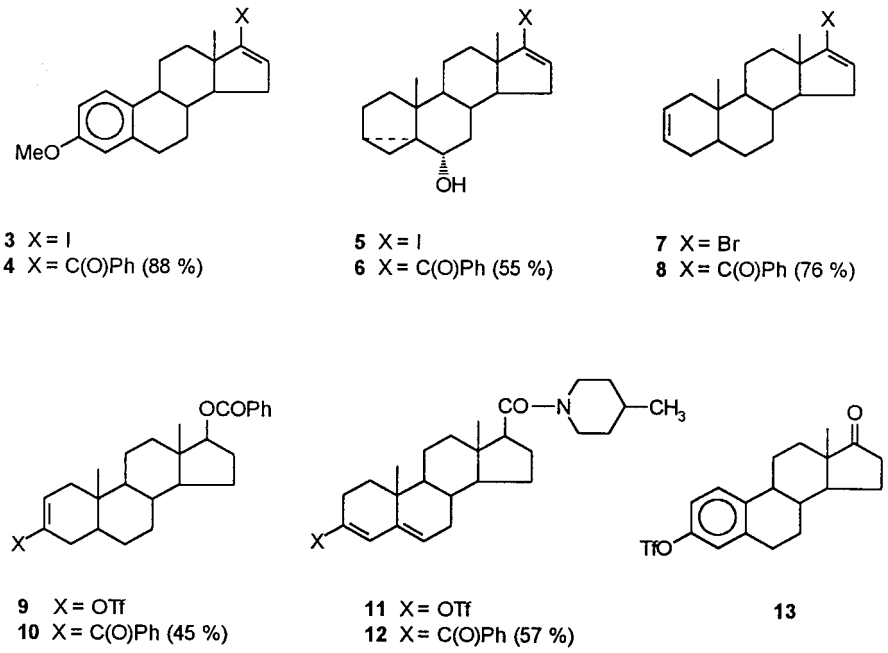

Figure 1. Carbonylation of other steroidal substrates.

Experimental

General procedure for the carbonylation reaction

The steroidal alkenyl halide or enol triflate (1 mmol) was reacted with $NaBPh_4$ (1 mmol) and carbon monoxide in the presence of $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol) and Et_3N (0.5 ml) in toluene at 90°C for 6–8 h. The reaction was monitored by GC or TLC. When the carbonylation was complete, the volatile components were removed in vacuo. The residue was dissolved in 30 ml of $CHCl_3$, washed with 30 ml 5% HCl, 30 ml of saturated aqueous $NaHCO_3$ and 30 ml of brine and dried over Na_2SO_4. Evaporation of the solvent and chromatography (silicagel, chloroform/methanol=98/2) gave the products.

17-Benzoyl-androst-16-ene (2). ^{1}H NMR δ 7.67 (d, J=7.6 Hz, 2H, o-Ph); 7.48 (t, J=7.6 Hz, 1H, p-Ph); 7.38 (t, J=7.6 Hz, 2H, m-Ph); 6.38 (m, 1H, 16-H); 1.2–2.4 (m, 22H, ring protons); 1.06 (s, 3H, 18-H_3); 0.82 (s, 3H, 19-H_3). ^{13}C NMR δ: 194.4 (CO); 153.9 (C-17); 146.2 (C-16); 139.4; 131.7; 129.0; 129.0; 128.0; 128.0; 56.5; 55.3; 47.6; 47.3; 38.5; 36.5; 34.4; 33.8; 32.8; 32.1; 29.1; 29.0; 26.8; 22.1; 20.6; 16.2 (C-18); 12.2 (C-19). MS m/z 362 (M^+)/80; 347/15; 257/30; 105/100; 77/30. IR (cm^{-1}) 1680 (C=O). Anal. Calcd for $C_{26}H_{34}O$: C, 86.13; H, 9.45. Found: C, 85.97; H, 9.56. Colourless needles, mp 158°C, yield: 345 mg (95%).

17-Benzoyl-3-metoxy-estra-1,3,5 (10),16-tetraene (4). ^{1}H NMR δ 7.71 (d, J=7.6 Hz, 2H, o-Ph); 7.47 (t, J=7.6 Hz, 1H, p-Ph); 7.39 (t, J=7.6 Hz, 2H, m-Ph); 7.12 (d, J=8.8 Hz, 1H, 2H); 6.70 (dd, J=8.8, 2.8 Hz, 1H, 1-H); 6.63 (d, J=2.8 Hz, 1H, 4-H); 6.42 (m, 1H, 16-H); 3.75 (s, 3H, OCH_3); 1.2–3.0 (m, 13H, ring protons); 1.08 (s, 3H, 18-H_3). MS m/z 372 (M^+)/100; 357/10; 267/15; 173/65; 105/90; 77/42. IR (cm^{-1}) 1675 (C=O). Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.95; H, 7.42. Pale yellow powder, mp 175°C, yield: 327 mg (88%).

17-Benzoyl-6α-hydroxy-3α,5α-cycloandrost-16-ene (6). ^{1}H NMR δ 7.67 (d, J=7.6 Hz, 2H, o-Ph); 7.48 (t, J=7.6 Hz, 1H, p-Ph); 7.38 (t, J=7.6 Hz, 2H, m-Ph); 6.37 (m, 1H, 16-H); 3.22 (m, 1H, 6-H); 1.2–2.4 (m, 17H, ring protons); 1.04 (s, 3H, 18-H_3); 0.94 (s, 3H, 19-H_3); 0.52 (m, 1H, 4-H_a); 0.28 (m, 1H, 4-H_b). MS m/z 376 (M^+)/3; 358/10; 105/52; 77/30; 57/100; 43/83. IR (cm^{-1}) 1680 (C=O). Anal. Calcd for $C_{26}H_{32}O_2$: C, 82.94; H, 8.57. Found: C, 83.05; H, 8.43. Pale yellow powder, mp 135°C, yield: 208 mg (55%).

17-Benzoyl-androsta-2,16-diene (8). ^{1}H NMR δ 7.70 (d, J=7.6 Hz, 2H, o-Ph); 7.47 (t, J=7.6 Hz, 1H, p-Ph); 7.39 (t, J=7.6 Hz, 2H, m-Ph); 6.39 (m, 1H, 16-H); 5.59 (m, 2H, 2-H, 3-H); 1.2–2.4 (m, 18H, ring protons); 1.08 (s, 3H, 18-H_3); 0.80 (s, 3H, 19-H_3). MS m/z 360 (M^+)/65; 345/10; 255/25; 105/100; 77/25. IR (cm^{-1}) 1680 (C=O). Anal. Calcd for $C_{26}H_{32}O$: C, 86.62; H, 8.95. Found: C, 86.45; H, 8.81. Pale yellow powder, mp 171°C, yield: 275 mg (76%).

3-Benzoyl-17β-(benzoyloxy)-androst-2-ene (10). ^{1}H NMR δ 8.00 (d, J=7.5 Hz, 2H, O(CO)Ph (o)); 7.77 (d, J=7.6 Hz, 2H, COPh (o)); 7.57 (t, J=7.5 Hz, 1H, O(CO)Ph (p)); 7.51 (t, J=7.6 Hz, 1H, COPh (p)); 7.40 (m, 4H, COPh+O(CO)Ph (m)); 6.46 (m, 1H, 2-H); 4.80 (m, 1H, 17-H); 1.0–2.5 (m, 20H, ring protons); 0.92 (s, 3H, 18-H_3); 0.78 (s, 3H, 19-H_3). MS m/z 482 (M^+)/32; 377/2; 360/4; 105/100; 77/22. Anal. Calcd for $C_{33}H_{38}O_3$: C, 82.12; H, 7.94. Found: C, 82.28; H, 7.83. Pale yellow powder, mp 145°C, yield: 215 mg (45%).

3-Benzoyl-17β-(3′-methyl-pentan-1′,5′-diyl)carboxamido-androsta-3,5-diene (12). ^{1}H NMR δ 7.75 (d, J=7.6 Hz, 2H, o-Ph); 7.51 (t, J=7.6 Hz, 1H, p-Ph); 7.38 (t, J=7.6 Hz, 2H, m-Ph); 6.61 (m, 1H, 4-H); 5.72 (m, 1H, 6-H); 4.60 (m, 2H, NCH_2); 3.95 (m, 2H, NCH_2); 1.2–3.0 (m, 23H, ring protons); 0.92 (s, 3H, 18-H_3); 0.88 (d, Hz, 3H, 3′-H_3); 0.81 (s, 3H, 19-H_3). MS m/z 485 (M^+)/52; 470/43;

154/40; 105/100; 77/23. IR (cm^{-1}) 1610 (C═O); 1685 (C═O). Anal. Calcd for $C_{33}H_{43}NO_2$: C, 81.60; H, 8.92; N, 2.88. Found: C, 81.25; H, 9.12; N, 3.02. Pale yellow powder, mp 129°C, yield: 275 mg (57%).

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