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SYNTHESIS OF THE ANTI-PROSTATE CANCER DRUG ABIRATERONE ACETATE

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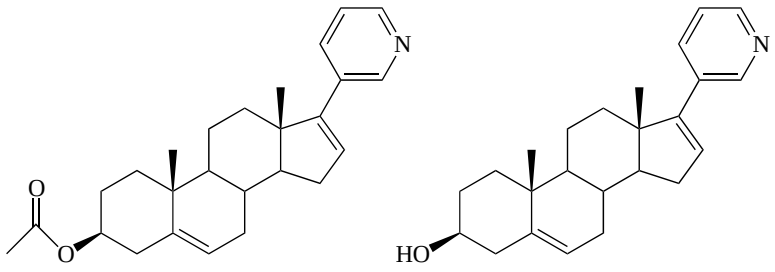
Abstract – Abiraterone acetate is used for the treatment of castration-resistant prostate cancer. Abiraterone acetate was synthesized from dehydroepiandrosterone via a three-step reaction including the formation of tosylhydrazone, cross-coupling reaction and acetylation, and a two-step purification including column chromatography and recrystallization with an overall yield of 51.9%. Here, an improved procedure for the preparation of abiraterone acetate is described. This synthetic process is of easy operation and low cost, which is suitable for industrialization.

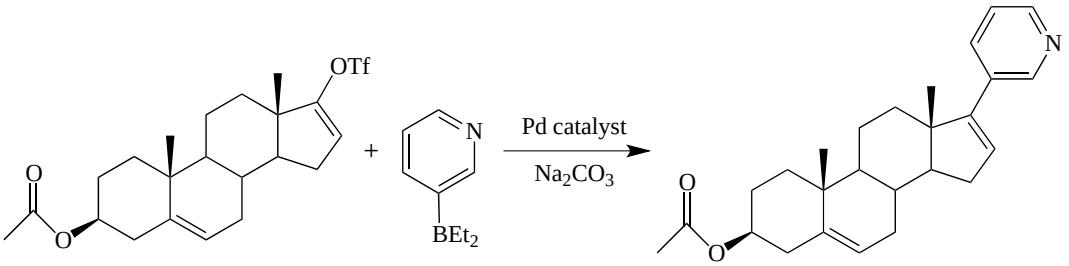
3β-Acetoxy-17-(pyrid-3-yl)androsta-5,16-diene (abiraterone acetate, **1**) is a prodrug for 17-(pyrid-3-yl)androsta-5,16-dien-3β-ol (abiraterone, **2**) which is used for the treatment of metastatic castration-resistant prostate cancer (**Figure 1**). It is marketed as Zytiga in the United States and is a potent inhibitor of human cytochrome P45017α (steroidal 17α-hydroxylase-C17,20-lyase).[1,2]



1 **2**

Figure 1. Abiraterone acetate (**1**) and abiraterone (**2**)

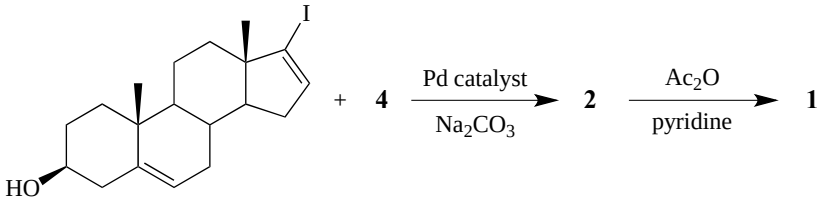
The original method[3] to synthesize **1** adopts the Suzuki coupling reaction of 17-enol triflate (**3**), derived from 3-acetate of dehydroepiandrosterone and triflic anhydride, with diethyl(pyrid-3-yl)borane (**4**) (**Figure 2**). This route is associated with high production cost, and formation of by-product such as androsta-3,5,16-trien-17-yl triflate. Previously, one improvement[4] was made to adopt the triethylamine (TEA) rather than the expensive base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) during the reaction between triflic anhydride and dehydroepiandrosterone acetate (**6**, R=Ac) in order to reduce the production of by-products. In this method, though dehydroepiandrosterone acetate (**6**, R=Ac) could be crystallized and removed from the crude target compound **1** by recrystallization without using column chromatography, the yield and the purity are much lower.



3 **4** **1**

Figure 2. One method of synthesis of abiraterone acetate (**1**)

The key step of another route reported[5] is the Suzuki coupling reaction based on 17-iodo-androsta-5,16-dien-3β-ol (**5**) with **4**. However, coupling with the iodide was much slower, which requires 4 days to complete this reaction, and it is hard to obtain the pure compound **1**, the impurities in the crude product only could be separated via reverse phase column chaomatography (**Figure 3**).



5

Figure 3. Another method of synthesis of abiraterone acetate (**1**)

In another reported route,[6] **5** was also coupled with 3-bromopyridine (**8**) with the existence of butyllithium. Cryogenic conditions are indispensable for reducing by-products. In addition, another drawback of this method is the use of column chromatography for purification.

The *N*-sulfonylhydrazones have been applied widely in organic synthesis for over sixty years, especially

used in the preparation of diazo compound through Bamford-Stevens reaction.[7] Over the last decade, the palladium-catalyzed cross-coupling between sulfonylhydrazones and aryl halides has been established and applied widely in organic synthesis.[8] Based on our interest in the functionalization of *N*-sulfonylhydrazones,[9] we described a protocol to access **2** (**Figure 4**). Our aim was to develop a simple and efficient new method for preparation of abiraterone acetate (**1**). This method was sensible for its simple industrial art, moderate operating condition and high yield.

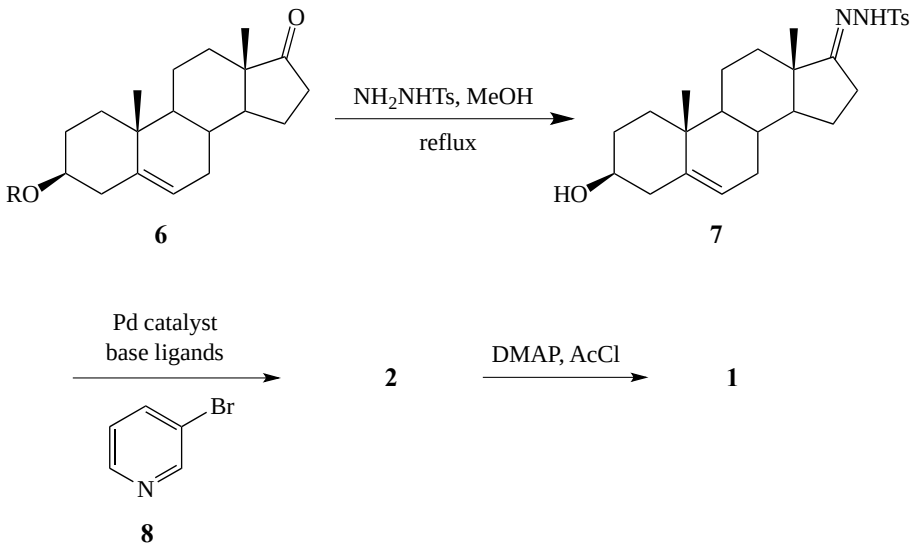
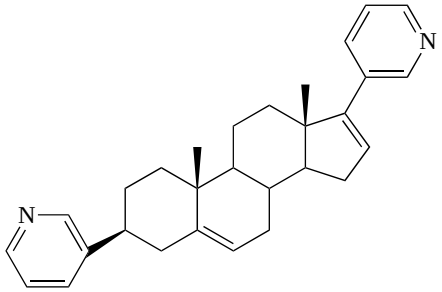


Figure 4. The new method of synthesis of abiraterone acetate (**1**)

Differed from other reported routes, the present method involves Bamford-Stevens reaction using dehydroisoandrosterone-17-*N*-toluenesulfonylhydrazone (**7**) as an intermediate compound instead of **5** or **3**. The rationable for choosing **7** over **5** and **3** was due to the reduction of by-product, these known forms of impurity such as androsta-3,5,16-trien-17-yl triflate and bis-steroidal compound were not formed due to the totally different mechanism. Furtherly, the cost advantage of 3-bromopyridine is obviously over diethyl(pyrid-3-yl)borane in the two reported methods.

On the basis of our experience and related literature, we began the study in examining the reaction between **7** and **8**. In an initial attempt, the target product **2** was obtained in 21.7% yield when using $Pd(OAc)_2$ as the catalyst and Li*O*t*Bu* as the base and Xphos as the ligand. By contrast, the reaction time of this present mehtod is quite longer than these reported routes, it requires 18 hours at 110 °C to complete this reaction as compared with the 5 hours required when the compound **3** was used. Even worse, what indicated the very low conversion rate was that there was still a lot of ingredient left. This result was actually unacceptable and we almost gave this method up. However, to our delight, the yield was obviously increased to 32.8% when using $Pd(PPh_3)_4$ as the catalyst.

The strong base and prolonged reaction time required for the cross-coupling reaction had enabled a side-reaction to occur between the product **2** and the ingredient compound **8** to form a by-product. The by-product was compound **9** (**Figure 5**). Whereas column chromatography on silica-gel of crude **2** afford pure **9** which was eluted first. Compound **9** was not able to be removed completely by recrystallization. Fortunately, the yield of this impurity was commoly under 10%, and it was easily reomved from the crude compound **2** via column chromatography.



9

Figure 5. The by-product compound **9**

During our development work, for the preparation of **2** using palladium-catalyzed cross-coupling of **7** with **8**, our emphasis was on selection of solvent, base, ligand and catalyst.

Catalysts. Different palladium catalysts such as $Pd(PPh_3)_2Cl_2$, palladium(II) acetylacetonate, and palladium(II) acetate and several others were attempted for this cross-coupling reaction, and the results are summarized in Table 1. As mentioned earlier, when employing $Pd(OAc)_2$ as a catalyst the target compound **2** could be isolated in 21.7% yield (entry 1), and $Pd(PPh_3)_4$ could increase the yield to 32.8% (entry 3). Compared with $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ could slightly increase the yield and reduce reaction time (entry 2). While the reaction efficiency dropped acutely when $PdCl_2$(dppf) as a catalyst was employed (entry 5). However, the reaction with palladium hydroxide and palladium chloride did not go to completion though we increased the loading of catalyst and reaction time (entries 4 and 7). Either $Pd(acac)_2$ or $PdCl_2(MeCN)_2$ resulted in an acceptable yield (entries 6 and 8). In addition, the reaction gave the best total yields of 51.9% when $Pd_2(dba)_3$ was used as a catalyst.

Table 1. Effect of catalysts for cross-coupling reaction[α]

Entry	Catalyst	Quantity (equiv)	Time (h)	Yield (%)	Remainder (%)	Impurity (%)
1	$Pd(OAc)_2$	0.01	18	21.7	68.6	7.8
2	$Pd(PPh_3)_2Cl_2$	0.01	20	28.6	60.4	8.3
3	$Pd(PPh_3)_4$	0.01	17	32.8	57.2	8.5
4	$PdCl_2$	0.03	30	-	90.7	7.3

5	$PdCl_2(dppf)$	0.02	26	16.2	73.9	6.7
6	$Pd(acac)_2$	0.01	20	39.6	50.2	7.7
7	$Pd(OH)_2$	0.03	30	-	89.9	8.1
8	$PdCl_2(MeCN)_2$	0.01	24	31.7	56.6	6.8
9	**$Pd_2(dba)_3$**	**0.01**	**24**	**51.9**	**38.2**	**8.4**

[α]Standard conditions: 1,4-dioxane (6 vols), LiO*t*Bu (0.7 equiv), Xphos (0.02 equiv), **7** (1.1 equiv), **8** (1.3 equiv), Reaction temperature (110 °C)

Solvents. Different solvents were screened for this cross-coupling reaction, and the resluts are summarized in Table 2. The reported solvent[10] for this type of reaction was 1,4-dioxane, and it was found to be optimal among the represent solvents (entry 1). To our disappointment, the reaction failed to be conducted when using toluene as a solvent, probably owing to the poor solubility (entry 2). MeCN resulted in a terrible yield (entry 3), and THF furnished the product in a low due to the low reaction temperature of 75 °C (entry 4). Only did DME provide the final product an acceptable yield (entry 5).

Bases. Base played a significant role in Bamford-Stevens reaction. We tried our best to select the most suitable one for this reaction among the represent bases. The results are also summarized in Table 2. The reported base for this type of reaction is LiO*t*Bu,[11] and it really contributed to the reaction (entry 1). However, more by-product was obtained with the attempt to increase the loading of LiO*t*Bu to 1 equiv. Compared with LiO*t*Bu, NaO*t*Bu and KO*t*Bu failed to provide **2** in acceptable yields. Moreover, the yield of the impurity compound **9** obviously increased for these extreme alkalinty (entries 6 and 7). Worse, the reaction failed to be conducted when using Cs_2CO_3 or piperidine as the additive (entries 8 and 9).

Table 2. Effect of solvents and bases[α]

Entry	Solvent	Bases	Temp (°C)	Time (h)	Yield (%)	Remainder (%)	Impurity (%)
1	**1,4-dioxane**	**LiO*t*Bu**	**110**	**24**	**51.9**	**38.2**	**9.4**
2	toluene	LiO*t*Bu	110	20	-	100	-
3	MeCN	LiO*t*Bu	95	30	13.7	77.3	5.6
4	THF	LiO*t*Bu	75	20	-	100	-
5	DME	LiO*t*Bu	95	24	36.3	55.2	6.2
6	1,4-dioxane	NaO*t*Bu	110	24	24.7	59.6	13.7
7	1,4-dioxane	KO*t*Bu	110	24	23.6	58.5	16.4
8	1,4-dioxane	Cs_2CO_3	110	24	-	100	-
9	1,4-dioxane	piperidine	110	24	-	100	-

[α]Standard conditions: $Pd_2(dba)_3$ (0.01 equiv), Xphos (0.02 equiv), **7** (1.0 equiv), **8** (1.2 equiv)

Ligands. Various kind of ligands were added in the reaction including Xphos, Sphos, dppm and so on (Table 3). To our delight, about half of the represent ligands exhibited good reactivity (entries 1-3, 7, 9 and 11). The yield was signficantly diminished when using Binap or dppb as a ligand (entries 5 and 8). However, Dave Phos, DpePhos and dppm gave the same terrible results (entries 4, 6 and 10).

Table 3. Effect of ligands[a]

Entry	Ligand	Time (h)	Yield (%)	Remainder (%)	Impurity (%)
1	**Xphos**	**24**	**51.9**	**38.2**	**9.4**
2	JohnPhos	24	42.7	51.2	5.5
3	Sphos	20	32.3	59.6	6.7
4	Dave Phos	24	-	92.4	6.7
5	Binap	22	14.6	74.7	9.6
6	DpePhos	24	-	90.3	8.4
7	XantPhos	22	35.2	55.6	6.5
8	dppb	24	11.3	80.8	7.8
9	dppe	24	40.9	51.4	7.2
10	dppm	24	-	88.3	9.3
11	dppp	24	29.7	60.1	8.5

[α]Standard conditions: 1,4-dioxane (6 vols), LiO*t*Bu (0.7 equiv), $Pd_2(dba)_3$ (0.02 equiv), **7** (1.0 equiv), **8** (1.3 equiv), Reaction temperature (110 °C)

The optimal condition has been selected among those various reaction conditions. The target product was obtained in 51.9% when using $Pd_2(dba)_3$ as a catalyst and using 1,4-dioxane as a solvent together with using LiO*t*Bu and Xphos as base and ligand, the temperature was at 110 °C during this reaction.

In summary, a simple and efficient method for the preparation of abiraterone acetate with improved yield and less by-product is reported. And we have also discovered the optimized conditions. We anticipate that this approach will find applications in the preparation of abiraterone acetate. Futher improvement of this catalytic reaction is underway in our laboratory.

EXPERIMENTAL

General Experimental Procedure for the Preparation of Abiraterone Acetate. Reagents were uesd as such without purification. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) were recorded using a Bruker spectrometer. The chemical shift data are reported as δ (ppm) using tetramethylsilane as internal standard. Mass spectra were recorded using an Agilent 1200-6320 Ion Trap XCT instrument. HPLC analysis was

performed on a Shimadzu instrument with a UV detector (210 nm) using a Shimadzu Wondasil C18 (250 mm x 4.6 mm, 5 μm) column. Mobile phase A [prepared by mixture of MeOH and MeCN in the ratio (80:20 v/v)]: mobile phase B [water], flow 1 mL/min, gradient 65:35 (0-25 min), 90:10 (25-40 min), 65:35 (40-50 min), 65:35 (50-60 min).

Dehydroepiandrosterone-17-*N*-tosylhydrazone (7)

Into a 100 mL round-bottomed flask, fitted with a magnetic stirrer bar, was placed *p*-toluenesulfonyl hydrazide (0.931 g, 5 mmol) and dehydroepiandrosterone (**6**, R=H) (1.442 g, 5 mmol) and MeOH (40 mL), followed by 3 $mol \cdot L^{-1}$ sulfuric acid (3 M, 0.05 mL). The temperature was raised to reflux to get a clear solution, after stirring for 5 h, the color of solution turned to light green. Then water (40 mL) was added over a period of 10 min, then the reaction mixture was cooled to room temperature and poured into cold water (100 mL), and filtered. The precipitate was collected, washed with a mixture solution of water (40 mL) and MeOH (10 mL) for two times. The product was dried in oven at 70 °C for 2 h, to give 2.17 g (91.6%) of **7** as light green powders. mp **176-178** °C. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 1.05 (s, 3H, 19-CH_3), 1.07 (s, 3H, 18-CH_3), 2.26-2.30 (m, 2H, 16-2H), 2.42 (s, 24-CH_3), 3.51-3.58 (m, 1H, 3α-H), 5.39 (d, 1H, *J*=4.8 Hz, 6-H), 7.29 (d, 2H, *J*=7.8 Hz, Ts2-H, Ts6-H), 7.82 (d, 2H, *J*=8.4 Hz, Ts3-H, Ts4-H). **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 16.56, 19.37, 20.47, 21.58, 23.39, 25.98, 31.22, 31.30, 31.58, 33.69, 36.62, 37.20, 42.21, 44.74, 50.29, 53.60, 71.62, 120.92, 128.01, 128.28, 129.31, 129.94, 135.56, 141.07, 143.75, 171.63. ESI HRMS: calcd for $C_{26}H_{36}N_2O_3S$+Na 479.2339, found 479.2332.

17-(Pyrid-3-yl)androsta-5,16-dien-3β-ol (2)

A stirred solution of **7** (1.89 g, 4 mmol) in 1,4-dioxane (50 mL) in a 100 mL round-bottomed flask was purged with nitrogen and tris(dibenzylideneacetone)dipalladium(0) catalyst (0.0405 g, 0.044 mmol) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl ligand (0.0385 g, 0.076 mmol) were added. After sitrring for 10 min, to the resultant rufous solution was added lithium *tert*-butoxide (0.2227 g, 2.78 mmol) base, then sitrring for 5 min and **8** (0.5 mL, 5.31 mmol) was added. The flask was fitted with a reflux condenser and these were purged with nitrogen. The mixture was heated to the refluxing temperature (110 °C) in an oil bath pan with stirring for 24 h. The reaction was completed and the solution turned to orange from dark brown. The reaction mixture was cooled to room temperature. Then EtOAc (20 mL) and cold water (20 mL) was added slowly at low temperature (10 °C) into the reaction mixtures. The organic phase was separated and washed with water (3 x 10 mL), then the constituents were isolated and purified by column chromatography, with the ratio of MeOH to CH_2Cl_2 was 1:100 in developing agent. The solvent was removed by vacuum distillation and the purified product was dried with anhydrous sodium sulfate. The yellow powder was collected in a little beaker to give crude **2** (0886 g, 62.9%) as pale yellow crystals, mp 213-215 °C, lit.[12] **212-215** °C. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 0.95 (s, 3H, 19-CH_3), 0.97 (s, 3H, 18-CH_3), 3.41-3.63 (m, 1H, 3α-H), 5.32 (d, 1H, *J*=4.8 Hz, 6-H), 5.90 (s, 1H, 16-H), 7.12-7.18

(m, 1H, Py5-H), 7.58 (d, 1H, *J*=8.0 Hz, Py4-H), 8.37 (d, 1H, *J*=4.4 Hz, Py6-H), 8.54 (s, 1H, Py2-H). **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 16.56, 19.33, 19.41, 20.37, 30.47, 31.46, 31.62, 31.80, 35.28, 36.66, 37.22, 42.30, 47.35, 51.80, 57.57, 71.50, 121.24, 123.05, 129.28, 133.05, 133.78, 141.13, 147.67, 151.67. ESI HRMS: calcd for $C_{24}H_{31}NO$+H 350.2478, found 350.2477.

3β-Acetoxy-17-(pyrid-3-yl)androsta-5,16-diene (1)

A stirred solution of the product from the foregoing reaction (0.752 g, 2.05 mmol) in dry CH_2Cl_2 (30 mL) in a 100 mL round-bottomed flask was added triethylamine (0.5 mL, 2.76 mmol), 4-dimethylaminopyridine (1.37 mg, 0.01 mmol). Acetyl chloride (0.25 mL, 3.15 mmol) was added at 20-30 °C over a period of 15 min. The mixture stirred at room temperature for 2 h. After reaction completed, water (50 mL) was added and stirred for 10 min, and the pH was adjusted to 6-7 with 0.1 mol·L^{-1} aqueous $NaHCO_3$. The organic layer was separated, washed with water (3 x 20 mL), and then concentrated. To the product was added anhydrous MeOH (30 mL), and the solution was heated to reflux and treated with activated carbon (3 g) for 2 h. The reaction mixture was then cooled to room temperature and stirred for 2 h. Then the product was obtained through filtering and washed with 80% EtOH and dried under vacuum for 6 h to give pure **1** (0.745 g) as white crystrals. The total productivity of pure **1** was 51.9% (based on **6**: R=H), mp **143-145** °C, lit.[13] 144-145 °C. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 1.05 (s, 3H, 19-CH_3), 1.08 (s, 3H, 18-CH_3), 2.04 (s, 3H, CH_3CO_2), 4.58-4.66 (m, 1H, 3α-H), 5.42 (d, 1H, *J*=4.76 Hz, 6-H), 5.99 (s, 1H, 16-H), 7.22 (dd, 1H, J_1=4.8 Hz, J_2=7.8 Hz, Py5-H), 7.64 (d, 1H, *J*=7.9 Hz, Py4-H), 8.46 (d, 1H, *J*=4.6 Hz, Py6-H), 8.63 (s, 1H, Py2-H). **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 16.56, 19.29, 20.48, 21.44, 27.72, 30.37, 31.78, 35.27, 36.64, 37.02, 38.17, 47.35, 50.34, 57.46, 73.82, 122.16, 122.89, 132.87, 133.64, 140.62, 147.82, 147.96, 151.66, 170.38. ESI HRMS: calcd for $C_{26}H_{33}NO_2$+Na 392.2584, found 392.2575. The spectroscopic data of the final product from this procedure were identical with those reported for the product obtained by the route previously described.[14]

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