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Effect of Solvent on Stereoselectivity in Pd/C (Type 39K)-Catalyzed Hydrogenation of Methyl 3-Oxo-4-aza-5-androstene-17-carboxylate, A Key Intermediate for Finasteride and Dutasteride#

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Abstract:

Solvent effects were studied in the stereoselective hydrogenation of methyl 3-oxo-4-aza-5-androstene-17-carboxylate (7) using re-activated Pd/C (type 39K) as a catalyst to furnish methyl 3-oxo-4-aza-5-α-androstene-17-carboxylate (2a), a common key intermediate for finasteride (1a) and dutasteride (1b), and reaction conditions were optimized to provide the required isomer with better selectivity.

Introduction

Finasteride[1] (**1a**) and dutasteride[2] (**1b**) are potential synthetic 4-aza-steroid active pharmaceutical ingredients, useful as specific inhibitors of steroid type II 5α-reductases and as intracellular enzymes that convert the androgen testosterone into 5α-dihydrotestosterone[3] (DHT). These are commercially available in the market under the brand name of PROPECIA and DUAGEN, respectively, and are used for the treatment of benign prostatic hypertrophy. Finasteride (**1a**) and dutasteride (**1b**) have same steroidal skeleton and they differ in the nature of the substituent on the amide nitrogen (Figure 1).

A similar synthetic approach is reported in the literature[4] for these steroid derivatives **1a** and **1b**. Both molecules are accessed from **2a** whose saponification yields acid **3**, followed by condensation with appropriate alkyl amine in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to give **4**, which upon oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) yields the respective steroids **1a** and **1b** as shown in Scheme 1.

The process[5] for the preparation (Scheme 2) of the key intermediate **2a** involves sequential oxidative cleavage of **5** utilizing $KMnO_4$–$NaIO_4$ to give keto-acid **6** and its cyclization with ammonia to provide unsaturated cyclic amide **7**, which upon subsequent hydrogenation in the presence of platinum oxide catalyst affords diastereomers **2a** and **2b** in an 80:20 ratio.

Pd/C-catalyzed hydrogenation was also reported by some authors. However, the given selectivity could not be reproduced

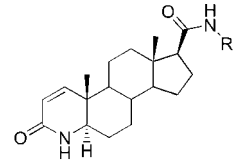
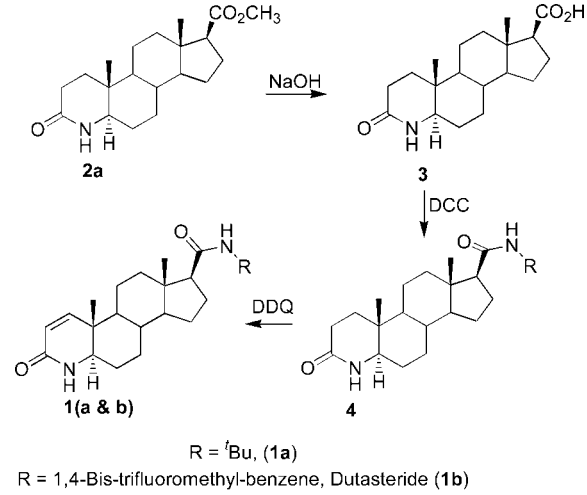


Figure 1. **APIs structural framework.**

Scheme 1. **Precedented Synthetic Approach**



Scheme 2. **Known synthetic route to advanced intermediate 2a**

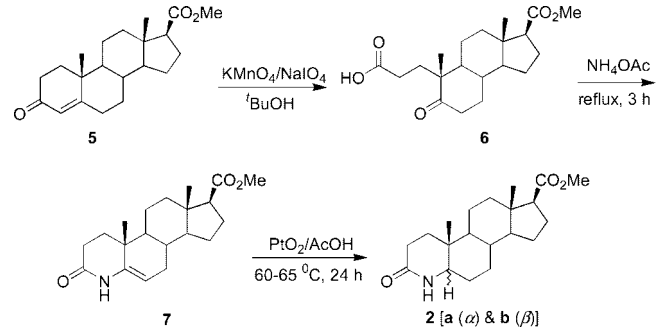


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Table 1. **Selective hydrogenation of 7 using Pd/C (type 39K) catalyst in different solvent mixtures**

							ratio by HPLC		
entry	solvent mixture	solvent (v/w[a])	Pd/C (%)[a]	time (h)	temp (°C)	yield (%)	**2a**	**2b**	**7**
1	IPA	200	60	12	70–80	95	92.5	4.3	1.3
2	MeOH	200	60	14	70–80	94.0	91.2	6.3	1.4
3	DCM	50	60	24	70–80	94.2	50.0	22.0	27.2
4	AcOH	20	60	35	70–80	83.4	70.6	20.0	6.0
5	IPA:AcOH	200:2	60	24	50–60	90.6	87.2	5.0	6.2
6	MeOH:AcOH	200:2	60	3	70–80	96.2	91.0	6.8	1.2
7	MeOH:AcOH	20:10	30	12	70–80	96.0	90.0	8.8	0.7
8	MeOH:AcOH	20:10	30	24	50–60	95.8	75.4	8.3	15.2
9	MeOH:AcOH	20:10	30	9	90–100	95.2	66.4	28.1	0.3
10	MeOH:AcOH	10:10	30	24	70–80	90.2	60.2	12.2	20.3
11	MeOH:AcOH	5:10	30	24	70–80	88.6	62.1	13.4	22.4

[a] Solvent (v/w) and Pd/C catalyst (%) are calculated with respect to (WRT) input material of **7**.

Table 2. **Solubility chart of 2a and 7 at different temperatures**

	solvents[a]											
	MeOH		IPA		AcOH		MeOH/AcOH (5:20)		MeOH/AcOH (20:20)		MeOH/AcOH (70:20)	
temp (°C)	**2a**	**7**	**2a**	**7**	**2a**	**7**	**2a**	**7**	**2a**	**7**	**2a**	**7**
75–35	+++	+	+++	++	++++	++++	+++	++	+++	++	++++	+++
40–45	++++	++	++++	++	++++	++++	+++	++	++++	++	++++	+++
50–55	++++	+++	++++	+++	++++	++++	++++	+++	++++	+++	++++	+++

[a] Notations used in case of solvents; + = very slightly soluble (10 mg/100 mL), ++ = slightly soluble (100 mg/100 mL), +++ = sparingly soluble (1 g/100 mL), and ++++ = soluble (1 g/30 mL).

in our laboratory when the reaction was conducted under literature conditions.[6a,b] In a recent modification[6c] of this process by conducting hydrogenation in the presence of catalytic amount of ammonium salts enhanced the selectivity of the desired α-isomer to 90%. However, usage of expensive PtO_2 in these processes made them commercially non-attractive.

Now we have taken up a comprehensive study of this hydrogenation reaction employing different grades of commercially available Pd/C catalysts. Effect of the solvent on selectivity was also studied.

Results and Discussion

It is known from the literature that there have been significant changes in the reactivity between different types of Pd/C catalysts towards a particular functional group.[7] We have screened[8] several types of Pd/C catalysts and found that the type 39K Pd/C catalyst works well in this reaction, resulting in >92% α-isomer selectivity, when the reaction was conducted in alcohols such as methanol, ethanol, and isopropanol as solvent medium without ammonium salts. There is no further improvement in isomeric excess by adding ammonium salts. The formation of desired α-isomer **2a** is extremely poor in other solvents such as acetic acid, dichloromethane, chloroform, and ethyl acetate (Table 1). The experiments conducted with chloroform and ethyl acetate provided trace amount of products (data not shown in Table 1).

These experimental results indicate that an alcoholic solvent is necessary to have better selectivity of **2a**. Because of the lower solubility of both **2** and **7**, larger quantities of alcoholic solvents were used for the reduction of **7**. In order to minimize the solvent quantity, we checked the solubility of both **2** and **7** in different combinations of alcohols and acetic acid mixture at different temperature conditions (Table 2).

It was found from these solubility experiments that compounds **2** and **7** are reasonably soluble in the combination of 20:10 alcohol (C_{1-3})/acetic acid at 50–60 °C. Also, the best selectivity was obtained by using 20:10 mixture of alcohols (C_{1-3}) and acetic acid[9] (Table 2). The other parameters such as Pd/C catalyst loading, time, and temperature were also optimized to minimum levels in order to make the process plant-friendly. Interestingly, it was also seen that when reactions were conducted at >80 °C the ratio of β-isomer **2b** is enhanced (approximately 25%). On the basis of these experimental results, we opted the following ideal conditions for this process (Scheme 3): (i) 20:10 methanol and acetic acid as ideal reaction medium, (ii) 30% Pd/C loading (WRT quantity of **7**), (iii) temperature at 70–80 °C, (iv) pressure at 9–10 kg/cm^2 (at 1 atm H_2 the reaction did not proceed well), and (v) 12–14 h of stirring. Further, a robust purification method was developed to purge the undesired β-isomer **2b** with good yield (85–90%). The detailed purification procedure is mentioned in Experimental Section.

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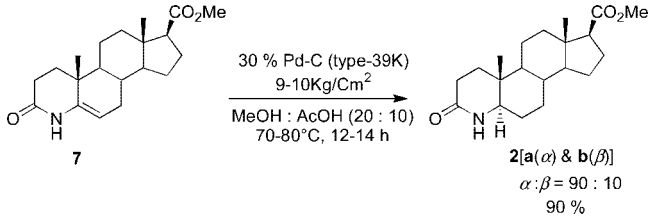
(8) There are three types of catalysts which were screened for this hydrogenation reaction beside type 39. No reduction was observed using types 5T487, 5T490, or 5T58.

(9) The compounds of **2** and **7** are soluble in minimum quantities of acetic acid (Table 2). Hence, acetic acid is directly used as a cosolvent along with methanol during the optimization of solvent quantity.

Scheme 3. **Stereoselective reduction: synthesis of key intermediate 2a**



In conclusion, we have studied the solvent effect on stereoselectivity in re-activated Pd/C (type 39K)-catalyzed hydrogenation of methyl 3-oxo-4-aza-5-androstene-17-carboxylate (**7**) to selectively furnish methyl 3-oxo-4-aza-5-α-androstane-17-carboxylate (**2a**), a key intermediate used in finasteride (**1a**) and dutasteride (**1b**) synthesis.

Experimental Section

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using 400 and 100 MHz, respectively, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The mass spectrum (70 eV) was recorded on HP-5989a LC-MS spectrometer. The melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without any purification.

Methyl 3-Oxo-4-aza-5-α-androstane-17-carboxylate (2a). A mixture of methyl-3-oxo-4-aza-5-androstene-17-carboxylate (**7**, 10 g, 0.03 mol), 5% palladium on activated carbon/type 39K (3.0 g), acetic acid (100 mL) and methanol (200 mL) was heated to 70–80 °C under a hydrogen pressure of 9–10 Kg/cm^2 in a closed autoclave system[10] for 12–14 h. The reaction mass was cooled to 50–55 °C and filtered through Hyflow to separate the catalyst, and the filter cake was washed with 10 mL of acetic acid. The combined filtrates were evaporated completely under vacuum to obtain the residue, which was crystallized from water (100 mL) to give 10 g of **2a** as a crystalline solid (α:β ~92:8).[11] The wet solid **2a** obtained was slurried in a mixture of acetone (50 mL) and concentrated HCl (10 mL) at 25–35 °C for 6–8 h. The resulting solid was filtered, washed with water (50 mL) till neutral pH (6–7) of mother liquor, and dried at 70–80 °C for about 8 h under reduced pressure to give compound **2a** as a white crystalline powder. Yield: 8.6 g (85%). Purity by HPLC: 99.12 % (no β isomer was observed). Mp: 290–295 °C (lit.[6] mp: 294–297 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.7 (bs, 1H), 3.69 (s, 3H), 3.07 (dd, J = 12.0, 4.0 Hz, 1H), 2.37–2.43 (m, 2H), 2.36 (t, J = 9.6 Hz, 1H), 2.14–2.16 (m, 1H), 2.00–2.03 (m, 1H), 1.23–1.95 (m, 11H), 0.98–1.12 (m, 1H), 1.13–1.14 (m, 1H), 0.93 (s, 3H), 0.83 (dt, J = 1.04, 3.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 172.5, 60.5, 55.2, 55.0, 51.1, 44.0, 37.9, 35.4, 35.0, 33.2, 29.4, 28.4, 26.9, 24.2, 23.4, 20.8, 13.4, 11.2. MS: m/e = 333 M$^+$.

Table 3. **Gradient profile**

time	0.0	30.0	50.0	55.0	60.0
A (%)	60.0	35.0	35.0	60.0	60.0
B (%)	40.0	65.0	65.0	40.0	40.0

Acknowledgment

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(10) A 1-L stainless steel autoclave and anchor-type agitator, designed for pressures of 20.0–30.0 kg/cm^2, manufactured by Chemee Equipment Pvt. Ltd., Mumbai, India, was used for the reaction.

(11) Isomeric excess of desired α-isomer **2a** was estimated by chiral HPLC analysis with kromasil 100 C_{18}, 250 mm × 4.6 mm, 5 μm. Mobile phase (MP): MP-A, 100% buffer (0.5 g of *o*-phosphoric acid in 1000 mL of water); MP-B, acetonitrile and water in the ratio of 70:30; 0.8 mL/min; 210 nm. See Table 3 for the gradient profile.