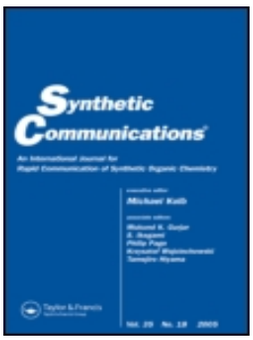

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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Diganta Baruah, Ram Nath Das & Dilip Konwar (2016) Facile green synthesis of 16-dehydropregnenolone acetate (16-DPA) from diosgenin, Synthetic Communications, 46:1, 79-84, DOI: 10.1080/00397911.2015.1121280

To link to this article: http://dx.doi.org/10.1080/00397911.2015.1121280

SYNTHETIC COMMUNICATIONS
2016, VOL. 46, NO. 1, 79–84
http://dx.doi.org/10.1080/00397911.2015.1121280

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Facile green synthesis of 16-dehydropregnenolone acetate (16-DPA) from diosgenin

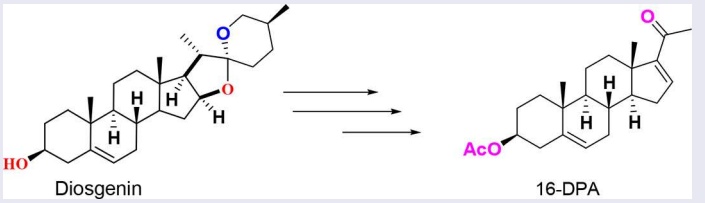
Diganta Baruah, Ram Nath Das, and Dilip Konwar

Synthetic Organic Chemistry Division, CSIR, Northeast Institute of Science and Technology, Jorhat, Assam, India

ABSTRACT

Chromium- and MnO_2-free green synthesis of industrially important steroidal drug intermediate 16-dehydropregnenolone acetate (16-DPA) starting from diosgenin is reported. The reaction sequence involves three steps: acetolysis followed by acetylation, oxidation, and hydrolysis. In the first step, Ac_2O was used both as reagent and solvent in combination with a Lewis acid ($AlCl_3$), which led to considerable reduction of high temperature and pressure requirements of earlier processes. The oxidation step was made catalytic with the use of $KMnO_4$(5 mol%) in the presence of co-oxidant $NaIO_4$, leading to less waste generation (of chromium, MnO_2, etc.). Minimization of the temperature, pressure, time consumption, and use of nontoxic solvents makes the process very handy and simple.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 9 October 2015

KEYWORDS
16-DPA; diosgenin; green synthesis

Introduction

Steroids are widely used drugs in the modern pharmaceutical industry. In spite of controversy about their side effects, the global markets of steroidal drugs and intermediates are worth more than a billion dollars. 16-Dehydropregnenolone acetate (16-DPA) **3** is widely used as central intermediate or building block for the synthesis of a large number of steroidal drugs including anabolic steroids, corticosteroids, sex hormones, and contraceptives.[1,2] Usually, 16-DPA (3β-acetoxy-pregna-5,16-dien-20-one) **3** is prepared from either of the two naturally occurring steroidal sapogenins, namely diosgenin (22-iso-5-spirostane-3β-ol) **1** and solasodine ((3β,22α,25 R)-spirosol-5-en-3-ol) **2**.[2–11] These compounds are extracted from *Dioscorea floribunda* and *Solanum Khasianum* tuber berries,

CONTACT Dilip Knowar dkonwar@yahoo.co.uk Synthetic Organic Chemistry Division, CSIR, Northeast Institute of Science and Technology, Jorhat 785006, Assam, India.
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respectively.[5,6] The conversion of diosgenin **1** to 16-DPA **3** was first reported by Marker and coworkers,[2–12] who discovered that the spiroketal ring system of diosgenin **1** and solasodine **2** could be opened by heating up the compounds with acetic anhydride in xylene solvent at 220 °C for 14 h at 5 bar pressure. The resultant pseudodiosgenin diacetate (3β,26-diacetoxyfurosta-5,20(22)-diene, PDA) **4** were then oxidized with $K_2Cr_2O_7$ to produce diosone (a keto ester) **5,** which on acid hydrolysis gave 16- DPA.

Later, many other processes were also reported. In most of the reported procedures, the acetolysis + acetylation step is carried out either using elevated temperature[5–12] or using acid catalysts such as HCl, *p*-TsOH, CH_3COCl, or crotonic acid to avoid the required elevated pressure.[11–16] Among the catalysts, pyridine / acetyl chloride or pyridinium hydrochloride were found to be superior.[14,15] On the other hand, oxidation of pseudodiosgenin diacetate **4** to diosone **5** is usually carried out using highly toxic CrO_3, $K_2Cr_2O_7$,[17] excess amount of $KMnO_4$,[18,19] etc. Obviously, the process produces huge quantity of nonreusable MnO_2 or chromic acid, which makes the workup procedure more tedious. Also the problems associated with the waste disposal often arise. Several other workers had also reported[11–15,20–23] the synthesis of 16-DPA and related compounds from different sapogenins, but the overall yields were only poor to moderate. Therefore, development of a better and handy procedure for the synthesis of 16-DPA, **3** can be considered as highly useful.

In this communication, we report a chromium- and MnO_2-free, efficient, and improved method for the synthesis of 16 DPA **3** from diosgenin **1**, eliminating the disadvantages of other reported procedures: (i) involvement of high temperature and pressure, (ii) requirement of toxic reagents in excess, (iii) production of hazardous waste, and (iv) requirement of a long reaction time.

Results and discussion

To develop an improved process, we first studied the acetolysis + acetylation of diosgenin **1** using different Lewis acids and conditions (Table 1). Studies on various Lewis acids, such as $ZnCl_2$, $FeCl_3$, $AlCl_3$, $InCl_3$, $NiCl_2$, and Cu $(OAc)_2$, showed that $AlCl_3$ is the most effective Lewis acid for this transformation with 98% yield of PDA (entry 3, Table 1). Use of $AlCl_3$ significantly shortened the reaction time as well as lowered the reaction temperature (entry 3, Table 1). The reaction could be the best carried out using a catalytic amount of anhydrous $AlCl_3$ in the presence of an excess of freshly distilled acetic anhydride (Scheme 1) that serves also as a solvent. The reaction was complete within 3 h by heating

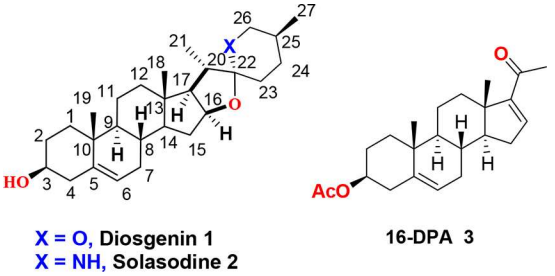


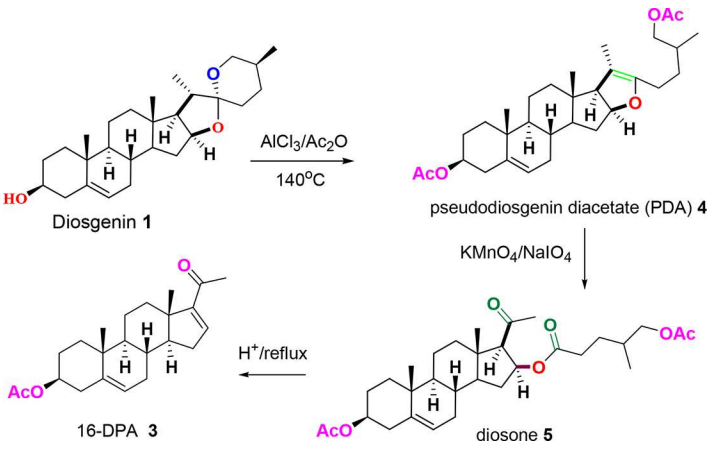
Figure 1. Structure of 16-DPA and its starting materials.

Table 1. Optimization of the Lewis acids for the synthesis of PDA **4** from diosgenin **1**.

No.	Lewis acids	Time (h)	Temperature (°C)	Yield (%)
1	$ZnCl_2$	6	160	45
2	$FeCl_3$	6	140	60
3	**$AlCl_3$**	**3**	**140**	**98**
4	$InCl_3$	6	160	40
5	$NiCl_2$	8	180	10
6	$Cu(OAc)_2$	8	180	40

at 140 °C under atmospheric pressure. After workup in ice-cold water, pseudodiosgenin diacetate **4** could be obtained in up to 98% yield. No side products such as monoacetylated or elimination products were observed.

The oxidation of PDA **4** to diosone **5** was carried out using $KMnO_4$ as oxidizing agent (Scheme 1).[24] To avoid the requirement of stoichiometric or excess oxidizing agent, it was decided to use a co-oxidant. Subsequently, co-oxidants including $NaIO_4$, $NaBrO_3$, $NaIO_3$, and $NaClO_4$ were screened (entries 1–11, Table 2). In the presence of $NaIO_4$, 5 mol% $KMnO_4$ was sufficient to complete the conversion (entries 2 and 3, Table 2). The optimized conditions (entry 4, Table 2) for oxidation of PDA to diosone are 1 mmol PDA, 0.05 mmol $KMnO_4$, 0.05 mmol $NaIO_4$, CH_2Cl_2/H_2O (1:1) solvent, and 3 h at room temperature. Enhancing the reaction time did not improve the product yield at all (entry 5, Table 2). Lowering the $KMnO_4$ loading from 0.05 mmol to 0.03 mmol instantaneously decreased the yield to 60% (entry 6, Table 2). Different solvents such as MeOH and THF neither enhanced the product yield nor increased the reaction rate (entries 7 and 8, Table 2). The optimized reactions were carried out using tetra ethyl ammonium bromide as a phase-transfer catalyst (PTC). The oxidizing system could be recycled up to 4 times, reducing excessive waste generation. Finally, diosone **5** was hydrolyzed using CH_3COOH to get 16-DPA **3.** The structure of 16-DPA **3** was confirmed by mixed melting-point determination and comparison of its FT-IR, NMR, and mass spectral data with an authentic sample.



Scheme 1. Synthesis of 16-DPA from diosgenin.

Table 2. Optimization of the reaction condition for the oxidation of PDA **4** to diosone **5**.

Entry	PDA/oxidant/co-oxidant ratio (mmol)	Solvent	Time (h)	Yield (%)
1	PDA/$KMnO_4$/$NaIO_4$ = 1:1:1	CH_2Cl_2	5	55
2	PDA/$KMnO_4$/$NaIO_4$ = 1:1:0.05	H_2O	5	45
3	PDA/$KMnO_4$/$NaIO_4$ = 1:1:0.05	CH_2Cl_2/H_2O = 1:1	3	75
4	**PDA/$KMnO_4$/$NaIO_4$ = 1:0.05:0.05**	**CH_2Cl_2/H_2O = 1:1**	**3**	**75**
5	PDA/$KMnO_4$/$NaIO_4$ = 1:0.05:0.05	CH_2Cl_2/H_2O = 1:1	5	75
6	PDA/$KMnO_4$/$NaIO_4$ = 1:0.03:0.05	CH_2Cl_2/H_2O = 1:1	4	60
7	PDA/$KMnO_4$/$NaIO_4$ = 1:0.05:0.05	MeOH/H_2O = 1:1	3	55
8	PDA/$KMnO_4$/$NaIO_4$ = 1:0.05:0.05	THF/H_2O = 1:1	3	50
9	PDA/$KMnO_4$/$NaIO_3$ = 1:0.05:0.05	CH_2Cl_2/H_2O = 1:1	6	62
10	PDA/$KMnO_4$/$NaBrO_3$ = 1:0.05:0.05	CH_2Cl_2/H_2O = 1:1	10	59
11	PDA/$KMnO_4$/$NaClO_4$ = 1:0.05:0.05	CH_2Cl_2/H_2O = 1:1	10	65

Conclusion

In summary, a practical and efficient chromium- and MnO_2-free green method for the preparation of 16-DPA is described starting from diosgenin. The process holds several advantages over the other conventional methods (Table 3). During the synthesis of PDA from diosgenin, the temperature and pressure requirements could be decreased drastically. Also the oxidation step was made catalytic, thus eliminating the accumulation of hazardous by-products (chromium, MnO_2, etc.). The operations in the process are useful in terms of yields, time, and generation of less toxic materials to the environment. Note that the catalyst used in the oxidation process is reusable. Because of the inherent simplicity, it is expected that the process can easily be exploited for industrial productions.

Experimental

Melting points are uncorrected. Reactions were monitored using thin-layer chromatography (TLC) on silica gel GF254. NMR spectra were recorded on Avance DPX 300-MHz FT-NMR spectrometer. Chemical shifts are expressed in δ units relative to

Table 3. Comparison of the developed method with the earlier reported methods.

Chemical steps	Conventional methods	Present method
1. Acetolysis + acetylation of diosgenin to PDA		
a. Reagent used	a. Acetic anhydride	a. Acetic anhydride with $AlCl_3$
b. Temperature	b. 200 °C	b. 140 °C
c. Pressure	c. 5 bar	c. Normal pressure
d. Reaction time	d. 14 h	d. 3 h
e Yield	e. 80–90%	e. 95–98%
f. Solvent	f. Xylene	f. Acetic anhydride
g. Apparatus	g. Autoclave or high-pressure instrument	g. Ordinary round-bottomed flask
2. Oxidation of PDA to diosone		
a. Reagent used	a. $K_2Cr_2O_7/CrO_3$	a. $KMnO_4$ with co-oxidant $NaIO_4$
b. Molar ratio of reagents	b. PDA : oxidizing agent (1:1.5 or more)	b. PDA : oxidizing agent (1:0.05: 0.05)
c. Temperature	c. 0–25 °C	c. 25 °C
d. Reaction time	d. 4–5 h	d. 3 h
e. Yield	e. 60–70%	e. 75%
f. Solvent	f. CH_2Cl_2	f. CH_2Cl_2 and water (1:1)
g. Side products	g. Toxicchromic acid, MnO_2, etc., in large quantity	g. Very little MnO_2 is formed as side products
h. Catalyst recyclability	h. Cannot be recycled	h. Can be recycled
i. Co-oxidant	i. No co-oxidant used	i. Co-oxidant used

tetramethylsilane (TMS) signal as internal reference. IR spectra were recorded using KBr pellets using a FTIR system 2000 Perkin-Elmer spectrometer. Mass spectra were recorded on Esquire 3000 mass spectrometer.

Synthesis of PDA 4

$AlCl_3$ (67 mg, 0.5 mmol) was added to Ac_2O (20 mL, freshly distilled) in a round-bottomed flask fitted with a $CaCl_2$ guard tube (drying tube). The mixture was stirred for 15 min at room temperature and then diosgenin **1** (414 mg, 1 mmol) was added. The reaction mixture was refluxed at 140 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was slowly poured into ice water (100 mL) with vigorous stirring. The mixture was kept at room temperature for 5 h, when the solid mass was separated. Filtration of precipitated solid and recrystallization from MeOH produced the product (488 mg, 98%) as white solid. Mp 98 °C (lit.[13,18,19] 98–100 °C); IR ($CHCl_3$): 1736 (broad), 1373, 1250, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.81(s, 3H), 0.97 (d, 3H, $J = 6.3$ Hz), 1.2 (s, 3H), 1.7 (s, 3H), 2.1(bs, 6H, acetate protons), 3.9 (d, 2H, $J = 4.5$ Hz), 4.80–4.45 (m, 2H), 5.62–5.31 (m, 1H); mass (*m/z*, 100%): 498 (M+).

Synthesis of 16-DPA 3

Pseudodiosgenin diacetate (PDA) **4** (498 mg, 1 mmol) and $NaIO_4$ (10.7 mg, 0.05 mmol) were dissolved in CH_2Cl_2 (20 mL) and H_2O (15 mL). To this mixture a solution of $KMnO_4$ (10 mg, 0.05 mmol) in water (5 mL) was added dropwise for a period of 10 min followed by triethyl benzyl ammonium chloride (TEBA, 5 mg, 2.2 mol%) at pH 4. The reaction mixture was stirred vigorously for a period of 3 h at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted by addition of CH_2Cl_2 (50 mL) and passed through a pad of celite (5 g). The organic solvent was separated and dried under reduced pressure to get diosone **5** as a gummy material. Without further purification, the crude product was treated with CH_3COOH (20 mL) and refluxed for 4 h at 110 °C. After completion, the reaction mixture was poured in ice water and extracted with CH_2Cl_2. Separation of the organic layer, washing with 5% $NaHCO_3$, drying over anhydrous Na_2SO_4, and evaporation of the solvent gave the solid product, which on recrystallization produced 16-DPA **3** as a white solid (267 mg, 75% w.r.t. PDA). Mp 172 °C (lit.[13,18,19] 169–175 °C); IR ($CHCl_3$): 1731, 1661, 1373, 1248, 1137, 1037, 943 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.0 (s, 3H), 1.2 (s, 3H), 2.0 (s, 3H), 2.2 (s, 3H), 4.5 (m, 1H), 5.31 (m, 1H), 6.65 (m, 1H); mass (*m/z*, 100%): 356 (M+).

Acknowledgments

The authors acknowledge the director, CSIR–NEIST, Jorhat, Assam, and Pallab Pahari for their kind help.

Funding

The authors are also thankful to the Council of Scientific and Industrial Research, New Delhi, India, for funding NWP Projects CSC-0125 and MLP-3000/03.

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