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A One-Pot Efficient Process for 16-Dehydropregnenolone Acetate

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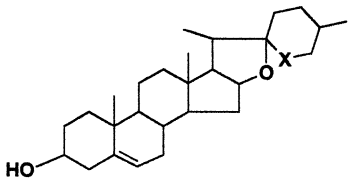
Abstract:
A one-pot eco-friendly and efficient transformation of steroidal sapogenin diosgenin (1) and solasodine (*2*) to a commercially very important drug intermediate 16-dehydropregnenolone acetate (16-DPA, 9) was developed with an overall yield of 75%. This process can easily be exploited for industrial production.

Introduction

16-Dehydropregnenolone acetate (16-DPA, **9**) finds increasing application as a versatile scaffold and building block for different steroidal drugs for it is an ideal platform for preparation of dexamethasone, β-methasone, 5α-reductase inhibitor, and related other steroidal pharmacophores.[1] 16-Dehydropregnenolone acetate (**9**) is best prepared either from steroidal sapogenin diosgenin (**1**) or from solasodine (**2**) obtained by extraction from naturally occurring *Dioscorea floribunda* or *Solanum khasianum* tuber berries, respectively.[2] Marker and co-workers first reported this transformation through acetolysis of diosgenin with acetic anhydride by autoclaving, oxidation, and eventually, acid hydrolysis of the oxidized product to afford 16-DPA without using any catalyst. Different acid catalysts, such as hydrochloric acid,

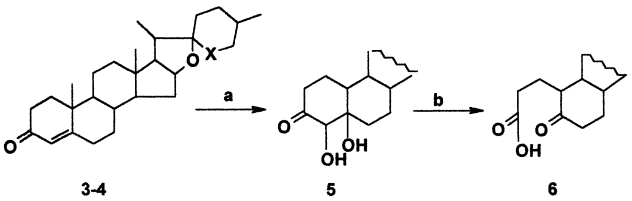


1&2

1.X= O, Diosgenin, 2. X= NH, Solasodine

octanoic acid, pyridine/acetyl chloride, ammonium chloride, and so forth, were examined in the above reaction later on. Subsequently, several other workers have reported[3−10] the synthesis of 16-DPA and related other compounds from different sapogenins but with low-to-moderate yield. Micovic et al.[11] have made an improvement through which 16-DPA could be prepared in 65−69% yield from diosgenin through acetylation without application of any pressure. In all the reports quoted above, the oxidizing agent used for the purpose of cleaving the double bond in the substituted furan ring of pseudodiosgenin or pseudosolasodine diacetate (**7**, Scheme 2) is chromium trioxide which is highly toxic.

Scheme 1



3-4 **5** **6**

3. X=NH, Solasodenone, 4. X=O, Diosgenenone a = $KMnO_4$, b =$NaIO_4$

Results and Discussion

Potassium permanganate,[12] an oxidizing agent used in organic chemistry for over a century and friendly to the environment, is one of the most versatile and vigorous of the commonly used oxidants and has been extensively used in acid, alkaline and neutral media. In 1978 Irismetov[13] et al. demonstrated that treatment of solasodenone (**3**) or diosgeninone (**4**) (a conjugated enone system) with potassium permanganate in water-*tert*-butyl alcohol solvent system attacks the 4,5 double bond to form a diol (**5**) which on further treatment with sodium periodate cleaves the diol to the corresponding keto acid (**6**) (Scheme 1). Now, in our programme for development of new process know-how for 16-DPA we have developed[14] for the first time a one-pot process for 16-dehydropregnenolone acetate (16-DPA, **9**) with more than 70% yield replacing the highly toxic chromium trioxide oxidizing agent by eco-friendly potassium permanganate in the presence of tetraethylammonium iodide under PTC conditions. Preparation of pseudodiosgenin diacetate or pseudosolasodine diacetate (**7**) was carried out by refluxing diosgenin or solasodine with acetic anhydride

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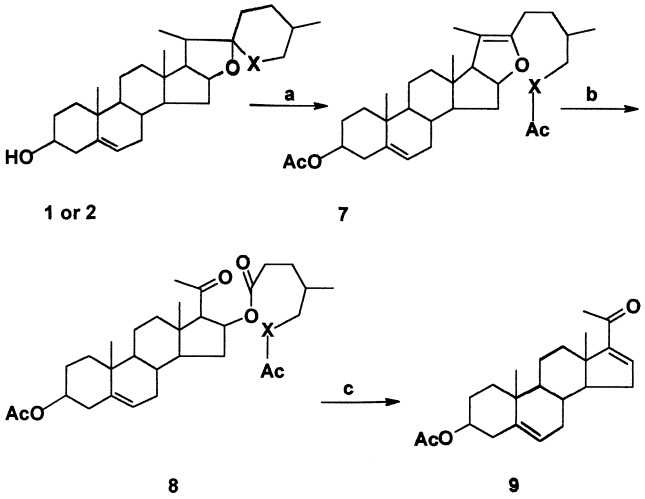
Scheme 2[a]



[a] Conditions: a. Ac_2O/AcCl, b. $KMnO_4/Et_4NI/C_2H_4Cl_2$ c. $NaOAc,3H_2O/C_2H_4Cl_2$.

in the presence of a catalytic amount of acetyl chloride at 138 °C in xylene solvent without application of any pressure. Use of acetyl chloride is advocated in catalytic amount for generation of acetate and hydrochloric acid,[15] and the hydrochloric acid thus produced then reacts with acetic anhydride to generate acetyl chloride and acetic acid for further acetylation. The oxidation of pseudodiosgenin diacetate/pseudosolasodine diacetate (**7**) with $KMnO_4$ in the presence of tetraethylammonium iodide was carried out under acidic condition (pH 3) at 0−5 °C. Cleaving of the double bond in the substituted furan ring exclusively takes place to form the keto ester (**8**) without formation of any diol. Under the above conditions the 5,6 double bond in (**1**) or in (**2**) is left completely untouched. (Scheme 2). The reaction probably follows the same path as described by Sharpless[16] (Scheme 3). It should proceed through the initial formation of a metallocyclooxetane (**10**) intermediate (a σ-metal complex) via [2 + 2] insertion of the olefinic π-bond of **7** in the substituted furan ring into a metal−oxo bond of manganese. Quite remarkably the other double bond in the 5,6 position of the steroid ring remained untouched under the reaction conditions, probably due to steric hindrance. Thus, in the oxidation of the double bond in the substituted furan ring of pseudodiosgenin or pseudosolasodine diacetate (**7**) by MnO_4^- the reaction should proceed with an oxo double bond, leading to conversion of a spectator oxo into an oxo triple bond (**11**), thus driving the formation of the cyclic manganate(V) diester (**11**) via rearrangement of (**10**). The ester (**11**) then breaks down to the product (**8**) and manganese dioxide. Hydrolysis of the keto ester (**8**) with sodium acetate trihydrate yields 16-DPA. We carried out the oxidation reaction in several other organic solvents starting from weakly polar to highly polar ones, keeping unchanged the other reaction parameters such as reaction time, temperature, and pH. Maximum yield (75%) of 16-DPA was obtained when the reaction was carried out in dichloroethane and dichloromethane followed

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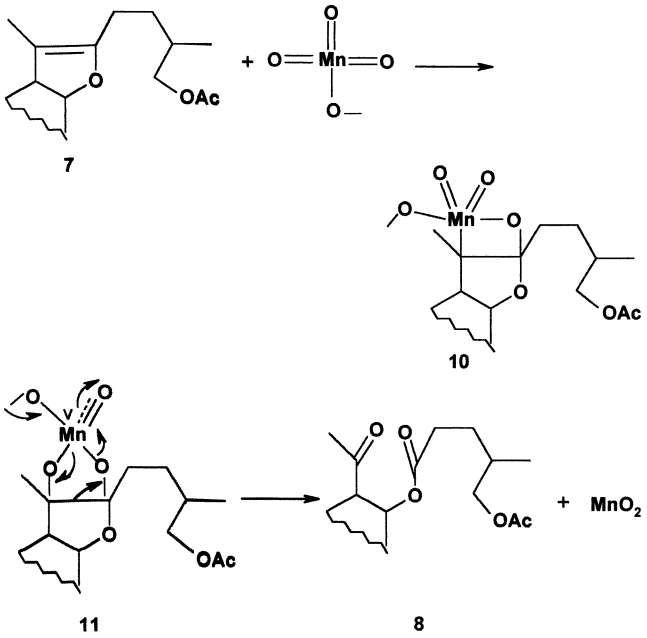
Scheme 3



by benzene. The yield of 16-DPA went down in polar solvents with worst result in acetone (<5%). Tetraethylammonium iodide (TEAI) was found to be superior to tetramethylammonium iodide (TMAI). This is significantly an alternative, one pot production of 16-DPA from the simplicity, expense, and eco-friendly point of view.

Conclusions

In summary, we achieved an efficient method for the preparation of 16-DPA, an extremely important intermediate for the synthesis of different corticosteroid drugs. The positive features of the method developed are (i) The reaction could be carried out in one pot to get the final product, (ii) no chromatographic purification was necessary throughout the synthesis, (iii) no exotic reagents were required, and (iv) the reagents used were less toxic to the environment, if compared to those of the method previously necessary.

The manufacturing process thus developed for the preparation of 16-DPA was indeed an alternative practical enough to be viable for industrial exploitation.

Experimental Section

Melting points were obtained with a Buchi apparatus and are uncorrected. Optical rotations were measured with Perkin-Elmer model 343 digital Polarimeter in chloroform solvent. Reactions were monitored on TLC on silica gel (60−120 mesh). The structure of 16-DPA prepared was confirmed by mixed melting point determination and comparison of its IR,^{1}H NMR, ^{13}C NMR, and mass spectral data with an authentic sample.

In 100 mL of acetic anhydride and 10 mL of acetyl chloride was heated 41.4 gm (0.1 mol) of diosgenin, under reflux in xylene for about 6 h at 138 °C until the TLC showed complete conversion of diosgenin. After that the reaction was cooled to 0 °C and 200 mL of 1,2-dichloroethane and 100 mL of water were added. The pH of the whole reaction

mixture was adjusted at around 3 by adding sodium acetate/acetic acid buffer. To this was added 0.5 gm of tetraethylammonium iodide. The whole reaction mixture was stirred, maintaining the temperature at around 0−5 °C. In 100 mL of water was dissolved 22.3 gm (0.14 mol) of potassium permanganate, and this was slowly added to the above reaction mixture under vigorous stirring in 30 min. Then the reaction mixture was stirred at room temperature for an extra hour. The progress of the reaction was monitored in TLC. Full conversion was found within 1.5 h. The keto ester (**8**) was extracted in 1,2-dichloroethane (2 × 200 mL), and the extracts were washed with water (2 × 250 mL) to remove any residual permanganate. Then 15 gm of solid sodium acetate was added to the organic phase, and the solvent was distilled off (4−5 h) azeotropically. Then the residue was cooled and added with about 300 mL of water to produce a solid product which was collected by filtration. The solid was thoroughly washed with water and was then crystallized from methanol to afford pure 16-dehydropregnenolone acetate (**9**). Yield = 26.56 (75%), mp 172°C, (lit.[2−4] 172−173°C), $[\alpha]^{D}_{25}$ −42° (*c* = 4 in $CHCl_3$), lit.[9] −39.5°. The above oxidation reaction was carried out in several other organic media, starting from weakly polar to highly polar solvents, keeping the other reaction parameters unchanged.

Table 1: **Effect of solvent and PTC in the yield of 16-DPA**

solvent	PTC	yield (%)
benzene	TEAI[a]	60
dichloromethane	TEAI	71
dichloroethane	TEAI	75
tetrahydrofuran	TEAI	31
acetonitrile	TEAI	55
acetone	TEAI	4.9
methanol	TEAI	35.2
ethanol	TEAI	29.5
dichloromethane	TMAI[b]	53.5

[a] Tetraethylammonium iodide. [b] Tetramethylammonium iodide.

The results are summarized in Table 1. The same procedure was followed to prepare it from solasodine to get an overall 75% yield of 16-DPA.

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