Esterification of tertiary alcohols in steroids under different conditions

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Abstract

Steroids can be made more lipid-soluble or more water-soluble simply by making suitable ester derivatives of hydroxyl groups. In this study, esterification of tertiary alcohols of cyproterone (CYP) and medroxyprogesterone (MPG) was comparatively conducted under different conditions. Several catalysts including basic and acidic ones such as dimethylaminopyridine (DMAP), *N*-methylimidazole, pyridine, 3-(1-methyl-2-pyrolidinyl) pyridine, and *N*-bromosuccinimide (NBS) were examined in the presence of appropriate acid anhydride or acyl chlorides. The results showed that NBS could be used as an effective catalyst for synthesis of propionate, butyrate, pentanoate, and hexanoate esters of CYP and MPG under mild conditions. The yield and the rate of the reactions were dependent on the chain length of substituted acyl groups. The yield ranged from 85% to 95% and the reaction time was between 10 and 12 h. Benzoate ester of CYP was also directly produced using CYP acetate and benzoic acid in the presence of sulfuric acid as catalyst.
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1. Introduction

Structure modification on drug molecules leads to changes in physicochemical and pharmaceutical properties such as absorption, solubility, and duration of action. Steroids can be made more lipid-soluble or more water-soluble simply by making suitable ester derivatives of hydroxyl groups. Derivatives with increased lipid solubility are often made to decrease the rate of release of the drug from intramuscular injection sites. More lipid-soluble derivatives also have improved skin absorption properties, and thus are preferable to dermatologic preparations [1].

CYP acetate (6-chloro-17-hydroxy-1α, 2α-methylene-4,6-pregnadien-3,20-dione 17α-acetate) is an antiandrogen and it is orally and topically used in the treatment of acne and hirsutism [2]. MPG acetate (17α-hydroxy-6α-metylpregn-4-ene-3,20-dione acetate) is used for treating many menstrual disorders [1]. The transdermal application of progestines has also become an increasingly popular research target during the last decade [3].

In this study on the modification of the structure of CYP (I) and MPG (II) their different esters were synthesized for improving topical application. In order to esterify the tertiary alcohol with sterical hindrance in CYP and MPG structures, we reviewed different esterification conditions for these alcohols. Many methods have been reported for acetylation of tertiary alcohols [4] under different conditions. CYP contains vulnerable groups such as 1, 2-cyclopropyl, 6-Cl, and 17α-OH. To maintain the pharmacological effects of the drug, the configuration of OH or OR (in ester form of CYP) should not be changed. Therefore, we need to find a desirable method for estrification to keep the stability of the structure. So, we selected several basic and acidic catalysts and compared these methods to find the best method for esterification of tertiary alcohols in steroids with sterical hindrance on OH.

2. Experimental

2.1. Material and reagents

All solvents and reagents were purchased from Sigma or Merck Chemical Companies. The products were purified by thin layer chromatography techniques. NMR spectra were recorded on a Brucker Avance DPX 250 MHZ instrument. Mass spectra were recorded on a Hewlett-Packard GC–MS.

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I. Cyproterone

II. Medroxyprogesterone
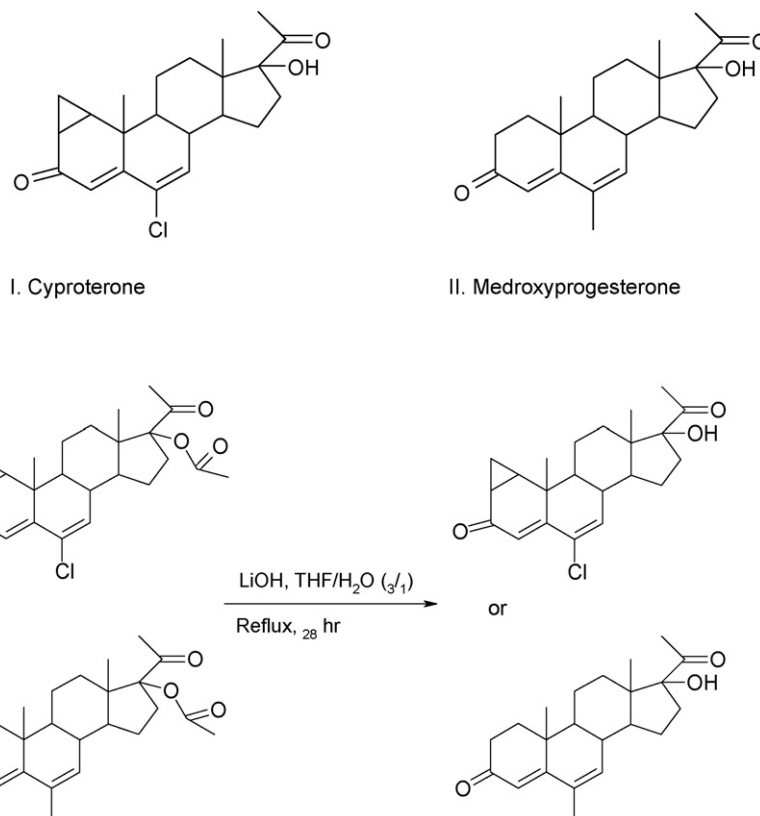
Scheme 1. Hydrolysis of CYP acetate and MPG acetate.

2.2. Preparation of CYP and MPG

As free alcohols forms of CYP and MGP are not commercially available, in the first step, free alcohols forms of CYP and MPG were prepared from CYP acetate and MPG acetate. Hydrolysis of 4 mmol of parent compound was done using 12 mmol of LiOH in 27 ml of THF–H_2O (3:1) at reflux temperature (Scheme 1) for 28 h [5]. After completion of the reaction,

Table 1
Acylation of CYP under different conditions

(1.1 mmol)
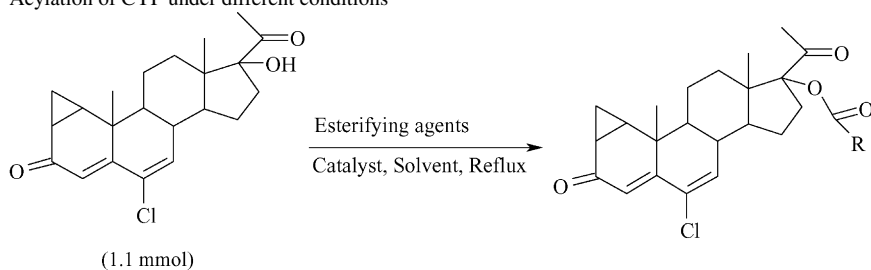
R=-$(CH_2)_n$-CH_3,   n=1,2,3,4

Entry	Esterifying agent (3.3 mmol) n = 1, 2, 3, 4	Catalyst	Solvent	Time (h)	Yield (%)
1–4	$(CH_3-(CH_2)_n-CO)_2O$	DMAP (3 mmol)	DMF	48	12–15
5–8	$CH_3-(CH_2)_n-COCl$	DMAP (3 mmol)	DMF	48	15–20
9–12	$(CH_3-(CH_2)_n-CO)_2O$	N-Methylimidazole (3 mmol)	DMF	48	32–37
13–16	$CH_3-(CH_2)_n-COCl$	N-Methylimidazole (3 mmol)	DMF	48	41–44
17–20	$(CH_3-(CH_2)_n-CO)_2O$	Pyridine (3 mmol)	Acetonitrile	48	13–16
21–24	$CH_3-(CH_2)_n-COCl$	Pyridine (2 mmol)	Acetonitrile	48	12–15
25–28	$(CH_3-(CH_2)_n-CO)_2O$	3-(1-Methyl-2-pyrrolidinyl)pyridine (2 mmol)	Pyridine	48	12–16
29–32	$CH_3-(CH_2)_n-COCl$	3-(1-Methyl-2-pyrrolidinyl)pyridine (2 mmol)	Pyridine	48	12–15
33–36	$(CH_3-(CH_2)_n-CO)_2O$	$CH_3-(CH_2)_n-COONa$ (3 mmol)	Acetonitrile	48	10–15
37–40	$(CH_3-(CH_2)_n-CO)_2O$	N-Bromosuccinimide (0.055 mmol)	Dried dichloromethane	10–12	70–85
41–44	$CH_3-(CH_2)_n-COCl$	N-Bromosuccinimide (0.055 mmol)	Dried dichloromethane	10–12	85–95

Table 2
Comparison of NBS with other catalysts under equal conditions
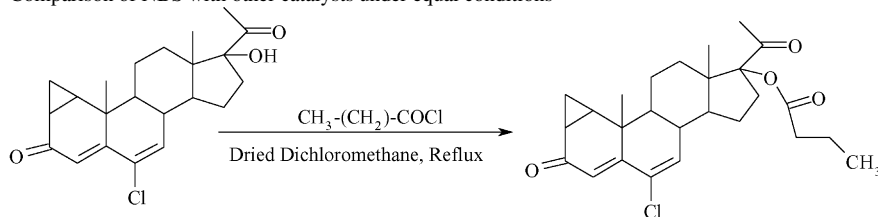
Entry	Catalyst	Time (h)	Yield (%)
1	N-Methylimidazole (3 mmol)	48	51
2	DMAP (3 mmol)	48	30
3	Pyridine (2 mmol)	48	28
4	3-(1-Methyl-2-pyrrolidinyl)pyridine (2 mmol)	48	32
5	N-Bromosuccinimide (0.055 mmol)	12	91
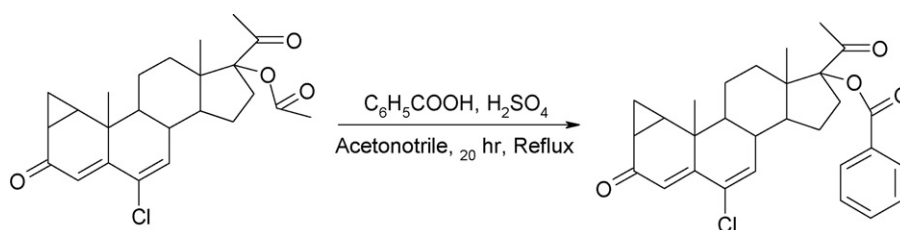
Scheme 2. Synthesis of CYP benzoate.

50 ml water was added to the reaction mixture and then the organic phase was decanted and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to obtain the product in 98% yield.

2.3. Synthesis of CYP esters

In order to prepare the esters of CYP, several esterification methods for tertiary alcohols described in the literature were evaluated [4].

In order to esterify CYP, we used appropriate anhydrides or acyl halides as esterifying agents, under conditions of basic and acidic catalysts. All the reactions were performed with 1.1 mmol of CYP and 3.3 mmol of esterifying agents and catalyst (the amounts of catalysts are shown in Table 1) under reflux condition, and the mixture was stirred until the starting material completely disappeared as monitored by TLC (Table 1). In order to compare NBS with other catalysts several reactions were done under equal conditions (Table 2).

CYP benzoate was directly synthesized using 1 mmol of CYP acetate and 4 mmol of benzoic acid in the presence of a few drops of sulfuric acid 98% in acetonitrile under reflux condition (Scheme 2). After completion, the reaction mixture was quenched with water and the crude product was extracted with CH_2Cl_2 and purified by thin layer chromatography, using hexane–ethyl acetate, 7:3.

2.4. Synthesis of MPG esters

Aliphatic esters of MPG were synthesized from 1 mmol of MPG and 3 mmol of appropriate acyl chloride using NBS as catalyst in dried CH_2Cl_2 under reflux condition (Table 3). The products were purified as mentioned above for CYP derivatives.

3. Results and discussion

It has previously been shown that tertiary alcohols are acylated with acid anhydride or acyl halides in the presence of catalytic quantity of Lewis acids and basic catalysts [4d,g]. In these reports, the catalysts are usually used for acetylation of alcohols. Panayiptis et al. showed that trimethylsilyl trifluromethansulfonate (TMSOTF) was only an extremely powerful catalyst [4f] for acetylation of OH in several steroids of a stable structure. Duan et al. also used [BMIm] BF$_4$ for acetylation of tertiary alcohols by acetic anhydride [4g]. This method is not appropriate for acylation of CYP and MPG, because these compounds are very insoluble in ionic solutions. There are no reports for acylation of sterically hindered tertiary alcohols of sensitive structures by other acylating agents.

First for optimization of the acylation conditions, many acidic and basic catalysts were evaluated. The esterification of CYP by using basic catalyst such as DMAP, N-methylimidazole, pyridine, and 3-(1-methyl-2-pyrrolidinyl) pyridine in the presence of appropriate anhydrides and acyl halides proceeded very slowly (Table 1, entries 1–33). We have also applied the salts of related carboxylic acids in the presence of the acid anhydrides. This reaction was also very slow (Table 1, entries 34–36). Therefore, an acid catalyst, NBS, was evaluated for the rapid and efficient acylation of CYP. The application of NBS as a catalyst in several chemical reactions is reported [6]. It has also been reported that NBS is an acid catalyst for acetylation of alcohols using acetic anhydride [7]. Therefore, we have used this acid catalyst

Table 3
Acylation of MPG with related acyl halides using NBS as catalyst
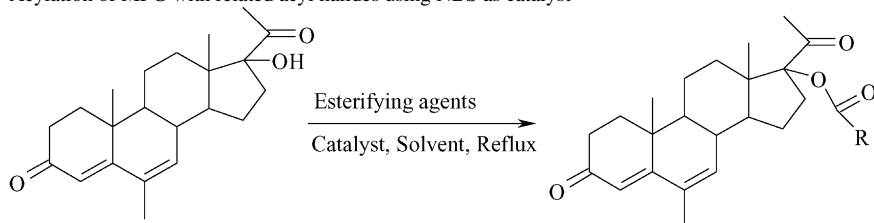
(1 mmol)

R= - $(CH_2)_n$- CH_3, n=1, 2, 3, 4

Entry	Esterifying agent (3 mmol)	Catalyst	Solvent	Time (h)	Yield (%)
1	CH_3–CH_2–COCl	N-Bromosuccinimide (0.055 mmol)	Dried dichloromethane	10	95
2	CH_3–$(CH_2)_2$–COCl	N-Bromosuccinimide (0.055 mmol)	Dried dichloromethane	10	95
3	CH_3–$(CH_2)_3$–COCl	N-Bromosuccinimide (0.055 mmol)	Dried dichloromethane	10	91
4	CH_3–$(CH_2)_4$–COCl	N-Bromosuccinimide (0.055 mmol)	Dried dichloromethane	12	85.5

for esterification of CYP using the acid anhydrides as well as acyl halides in dried dichloromethane. The results show that this reaction in the presence of appropriate acyl chlorids proceeds in less than 12 h to give 95% yield (Table 1, entries 37–44). In order to compare NBS with other catalysts the esterification of CYP was done in the presence of butyryl chloride and different catalysts under equal conditions (Table 2). The results show that NBS is a good catalyst under mild reaction condition in comparison with other catalysts (Table 2). We have used this catalyst for the preparation of CYP acetate, CYP propionate, CYP butyrate, CYP pentanoate, and CYP hexanoate. The yields and the rates of the reactions were dependent on the chain length of substituted acyl groups. In this study, we used NBS of the catalytic amount of 0.055 mmol for 1.1 mmol of alcohol that is less than the amount used by Xu and Karimi [7]. The results show that the esterification of these compounds has a higher yield and is also more rapid when acyl halides is used instead of acid anhydrides which were used by Karimi and Xu [7]. However, the actual role of NBS is not clear but Karimi et al. [7b] presented a mechanism in acetylation of alcohol, showing that NBS might act as a source for Br^+ which in turn activates the carbonyl group of Ac_2O to produce the highly active acylating agent (Scheme 3). According to this mechanism acyl halides acetylated the compounds more rapidly than anhydrides because Br^+ reacts with X^- from acyl halides and RCO^+ is more available for acylation reaction.

None of the acid and basic catalysts tested resulted in a reaction with an acceptable yield for the synthesis of CYP benzoate. Therefore, CYP benzoate was directly synthesized using CYP acetate and benzoic acid in the presence of a few drops of sulfuric acid 98% (Scheme 2). This reaction was carried out under reflux condition for 20 h to give 60% yield.

The acylation of MPG was also employed using NBS as catalyst under the same conditions used for acylation of CYP (Table 3).

In conclusion NBS has been employed as an effective catalyst for the acylation of sterically hindered tertiary alcohols in steroids of sensitive structures under mild reaction condi-
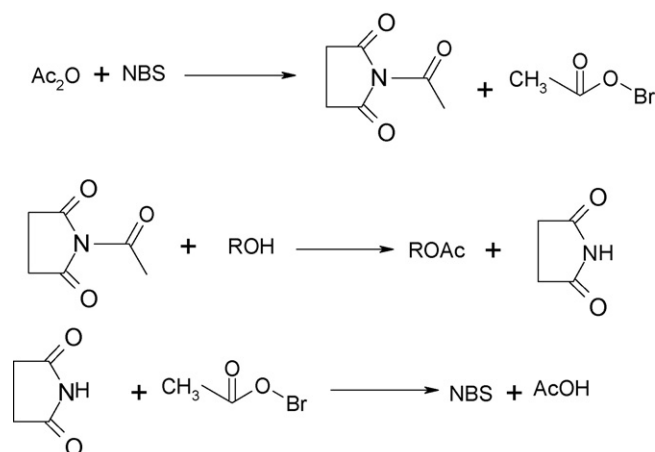
Scheme 3. The postulated mechanism of NBS catalysis [7b].

tions. As NBS was used only in catalytic amount, the reaction of NBS with alkene groups may be negligible. It has been reported that acetylation of optically active alcohols in the presence of NBS proceed well with complete retention of configuration [7b]. Therefore, the reactions proceeded well with complete retention of configuration of OH. This is important for pharmacological effects of steroids. This catalyst is not suitable for the preparation of aromatic esters.

Acknowledgments

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