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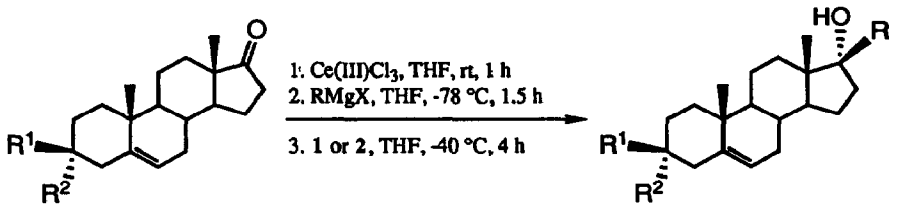
# Highly Efficient Nucleophilic Addition of Alkyl Grignard Reagents to 17-Ketosteroids in the Presence of Cerium(III) Chloride: Synthesis of 17α-Propyl-17β-Hydroxy-4-Androsten-3-one, An Androgen Receptor Antagonist

Xun Li, Shankar M. Singh* and Fernand Labrie*
Medicinal Chemistry Division, Laboratory of Molecular Endocrinology, CHUL Research Center, Québec City, Québec G1V 4G2, Canada

Abstract: The addition of alkyl Grignard reagents to sterically hindered 17-ketosteroids was significantly enhanced by anhydrous cerium(III) chloride with notable suppression of abnormal reactions, while the addition products were obtained in good to excellent yields and high stereoselectivity.

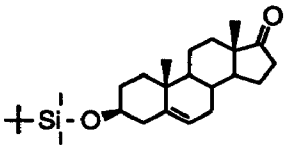
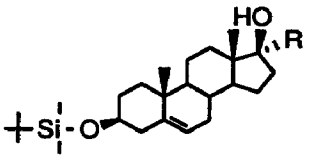
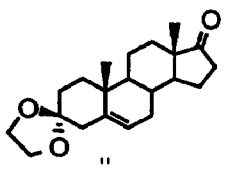
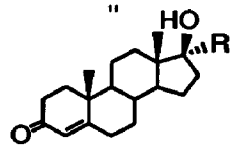
The prostate and skin are not only major sites of androgen action, but also sites of androgen metabolism. The most active natural androgen is 5α-dihydrotestosterone (DHT). Since DHT is implicated in the pathogenesis of benign prostatic hyperplasia (BPH) and prostatic cancer as well as in androgenic alopecia, acne vulgaris and hirsutism,[1] inhibition of androgen action by androgen receptor antagonists is a logical approach for the treatment of these conditions. A few compounds are currently undergoing clinical trials for such indications, including 17α-propylmesterolone (SH 434),[2a] chlormadinone acetate (CMA)[2b] and 17α-propyltestosterone (Win 17665).[2c-2e] All the above compounds have a 17α-substituent and it thus appears that steroids having an alkyl chain at 17α-position are potential antiandrogens.




1: R = alkyl chains, $R^1 = (CH_3)_3CSi(CH_3)_2O$-, $R^2$ = H
2: R = alkyl chains, $R^1 = R^2 = -OCH_2CH_2O-$

During the course of synthesis of steroidal compounds aimed at specific biological properties, we needed a method that could provide an efficient nucleophilic addition of alkyl metals to 17-ketosteroids. The nucleophilic addition of Grignard or lithium reagents to carbonyl compounds is undoubtedly one of the most versatile reactions known to chemists.[3] Moreover, it is also well known that the reaction of easily enolizable carbonyl compounds results mainly in the formation of enolates related to the strong basicity of alkali metal reagents. However, the desired products are difficult to obtain in satisfactory yields.[4] Furthermore, the reaction of hindered ketones with these reagents having a β-hydrogen gives mainly the reduction products.[4] Several

Table 1. The Reaction of 17-Ketosteroids with RMgX-Ce(III)$Cl_3$,[a] RMgCl and RLi.

| Entry | 17-Ketosteroid | Reagent | Product | Yield (%) |
|---|---|---|---|---|
| 1[b,c] |  | RLi<br>R = $(CH_2)_3CH_3$ |  | 41 |
| 2[d] | " | RMgCl<br>R = $(CH_2)_3CH_3$ | " | 0.0 |
| 3 | " | RMgCl-$CeCl_3$<br>R = $(CH_2)_3CH_3$ | " | 91 |
| 4 | " | RMgCl-$CeCl_3$<br>R = $CH_2C_6H_5$ | " | 96 |
| 5 | " | RMgCl-$CeCl_3$<br>R = $(CH_2)_2CH_3$ | " | 92 |
| 6 | " | RMgBr-$CeCl_3$<br>R = $(CH_2)_5CH_3$ | " | 88 |
| 7 | " | RMgCl-$CeCl_3$<br>R = $CH(CH_3)_2$ | " | 82 |
| 8[e] | " | RMgBr-$CeCl_3$<br>R = $(CH_2)_2CH{=}CH_2$ | " | 73 |
| 9[f] | " | RMgBr-$CeCl_3$<br>R = $(CH_2)_{11}OTHP$ | " | 72 |
| 10[g,h] |  | RMgCl<br>R = $(CH_2)_2CH_3$ |  | 0.0 |
| 11[h] | " | RMgCl-$CeCl_3$<br>R = $(CH_2)_2CH_3$ | " | 95 |
| 12[h] | " | RMgCl-$CeCl_3$<br>R = $(CH_2)_3CH_3$ | " | 94 |

[a] Unless otherwise noted, the RMgX-Ce(III)$Cl_3$ complex was prepared and the reactions were carried out as described in the standard procedure. [b] The 17-ketosteroid was prepared by treatment of 3$\beta$-hydroxy-5-androsten-3-one with *tert*-butyldimethylsilyl chloride and triethylamine in $CH_2Cl_2$ at room temperature (rt) for 24 hr. [c] The addition reaction was conducted at -78 °C for 1 hr, -20 °C for 2 hr and rt for 3 hr. [d] The reaction was stirred at -78 °C for 1 hr, rt for 12 hr and refluxed at 80 °C for 24 hr. [e] The RMgX was prepared from the corresponding 4-bromo-1-butene in diethyl ether at 0 °C for 15 min and rt for 1 hr. [f] The RMgX was prepared from the corresponding THP protected 11-bromo-1-undecanol in diethyl ether at rt for 0.5 hr and then 40 °C for 4 hr. [g] The reaction mixture was stirred at rt for 32 hr and then refluxed for 5 hr, which gave only the reduction product (65%). [h] After the addition reaction was complete, the mixture was treated with 9% aq. HCl followed by acetone (100 mL) and stirred for 12 hr.

methods have been developed to reduce abnormal products by changing solvents[5] or using additives.[6] While these reported methods are effective in some cases, they are not always efficient and lack general applicability.

Alternatively, the addition of organolithium or Grignard reagents to carbonyl compounds was remarkably enhanced by the assistance of lanthanides,[4c,7] particularly, in the presence of cerium(III) halides.[4a-4f] Indeed, the addition of methyllithium to the 17-ketosteroid in the presence of Ce(III)$Cl_3$ gave a very high yield of the

addition product.[4b,8] However, thus far, the addition of alkyllithiums or Grignard reagents having a $\beta$-hydrogen to 17-ketosteroids in the presence of cerium(III) halides has not been studied. Herein, we report that the addition of a wide variety of alkyl Grignard reagents to 17-ketosteroids in the presence of Ce(III)$Cl_3$ provides the desired addition products in high yields.

In order to select the best and easily available alkylating reagent, we first investigated the reactions of 17-ketosteroids with the *n*-BuLi, *n*-BuMgCl and *n*-BuMgCl-Ce(III)$Cl_3$ complex. We chose RMgX over RLi for the preparation of the Ce(III)$Cl_3$ complex, since RMgX is readily available or could be easily prepared on a large scale. The direct addition of *n*-BuLi to 17-ketosteroids **1** gave 41% of the addition product and 14% of the reduction product (entry 1). While the direct addition of *n*-BuMgCl did not provide the addition product, 22% of the reduction product was obtained instead (entry 2). However, when the *n*-BuMgCl-Ce(III)$Cl_3$ complex was used, a very high yield (91%) of the addition product was obtained (entry 3). It thus clearly appears that RMgX-Ce(III)$Cl_3$ is a reagent of choice (Table 1). Next, we tested the general applicability of this reagent with a wide variety of alkyl chains. Indeed, the addition of BnMgCl-Ce(III)$Cl_3$ complex gave a stereoselective product in excellent yield (entry 4). The reaction of 17-ketosteroid **1** with the 3-buten-1-ylmagnesium bromide-Ce(III)$Cl_3$ complex gave the 17$\alpha$-product in 73% yield (entry 8). The addition also gave a product in good yield, when longer alkyl chains having a functional group were utilized (entry 9). Even a hindered alkyl substituent gave the addition product in 82% yield (entry 7). Finally, we utilized the present method to achieve a simple synthesis of Win 17665, (17$\alpha$-propyltestosterone). Thus, addition of the propylmagnesium chloride-Ce(III)$Cl_3$ complex to 17-ketosteroid **2**, followed by acid hydrolysis, afforded the 17$\alpha$-propyltestosterone in excellent yield and high stereoselectivity.

In conclusion, the present method offers an easy way to introduce a wide variety of alkyl chains at the 17$\alpha$-position of 17-ketosteroids and provides an opportunity to prepare sufficient amounts of such compounds for their biological evaluation, a task that was difficult in the past.

Standard Procedure for the Addition Reaction: Anhydrous cerium(III) chloride (5.97 mmol) in freshly distilled tetrahydrofuran (80 mL) was stirred at room temperature for 1 hr. The mixture was cooled to -78 °C and alkylmagnesium chloride/bromide (5.97 mmol) was added and the mixture was stirred at -78 °C for 1.5 hr.[9] 17-Ketosteroids (0.995 or 1.218 mmol) in THF (40 mL) were cooled at -78 °C and were added to the above mixture. After addition, the mixture was stirred at -40 °C for 4 hr. The reaction was quenched with an aq. AcOH solution (2 mL of AcOH in 75 mL $H_2O$) and was warmed to room temperature. The mixture was then extracted with EtOAc (3 X 100 mL) and the combined organic phase was washed with brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the corresponding 17$\alpha$-hydroxy-17$\beta$-alkyl-testosterone analogues.[10]

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(8) Addition of 2-lithopropene in the presence of Ce(III)$Cl_3$ is also reported to give the addition product in high yield.[4e]

(9) It is believed that the temperature, during the preparation of RMgX-Ce(III)$Cl_3$ complex, is an important factor to insure a successful addition. In fact, the addition of 17-ketosteroid at -78 °C with RMgX-Ce(III)$Cl_3$ complex prepared at 0 °C or -20 °C, gave predominantly abnormal products.[4] While RMgX-$CeCl_3$ complex prepared at -78 °C gave the desired products. It thus appears that RMgX-Ce(III)$Cl_3$ species obtained at 0 °C or -20 °C were not the same as at -78 °C.

(10) The IR, EI-MS, $^1H$- and $^{13}C$-NMR (300 MHz) spectral properties of each of the 17$\alpha$-hydroxy-17$\beta$-alkyl steroidal analogues were consistent with the assigned structures.

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