STEROLS WITH MODIFIED SIDE CHAINS

by

Josef E. Herz and Esperanza Vázquez

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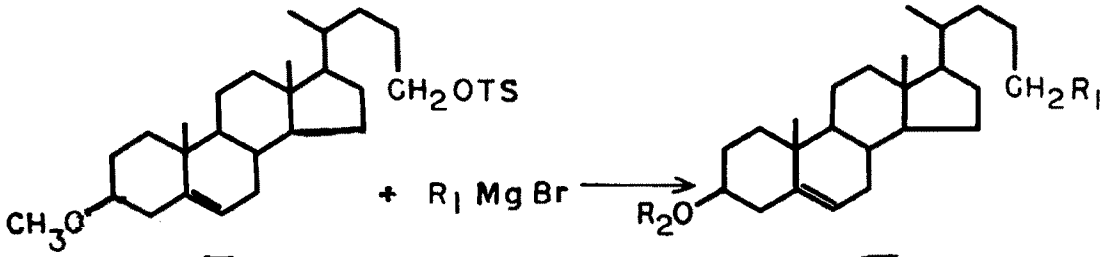
INTRODUCTION

Recently Fouquet and Schlosser[1] published an improved method for carbon-carbon linking by controlled copper catalysis, utilizing the reaction between a toluenesulfonate and a Grignard reagent in the presence of Li_2CuCl_4[2]. This method seemed to us advantageous for the preparation of sterols with modified side chains and we therefore applied this reaction to the synthesis of a number of representative sterols in order to determine the scope of this reaction.

CONCLUSIONS

As can be seen in Table 1 the reaction proceeds with good yield when the group R_1 of the Grignard reagent is n-butyl, isopropyl, cyclohexyl, phenyl. When the group was 1-adamantyl or allyl the 24-bromide[4] of the steroid was obtained exclusively. We intend to investigate this reaction further and to apply it to the synthesis of cholesterols deuterated in positions 25, 26 and 27.



R_1 MgBr I II

R_1	yield	R_2 = CH_3-	R_2 = H
a) n-butyl	81%	mp. 120-1°C $(\alpha)_D$ -32° Anal: $C_{29}H_{50}O$ Cal. C: 83.98 H: 12.45 found C: 83.74 H: 12.01	
b) isopropyl	78%	mp. 82-3°C lit[3] 84°C $(\alpha)_D$ -45°C lit -46° Anal: $C_{28}H_{48}O$ Cal. C: 83.92 H: 12.07 found C: 83.86 H: 12.12	mp. 145° lit 148° $(\alpha)_D$ -38° lit -39.5°
c) cyclohexyl	81%	mp. 102-3° $(\alpha)_D$ -30° Anal: $C_{31}H_{52}O$ C: 84.48 H: 11.89 found C: 84.27 H: 11.91	mp. 108-9°C $(\alpha)_D$ -25° $C_{30}H_{50}O$ C: 84.43 H: 11.81 found C: 84.51 H: 11.98
d) phenyl	85%	mp. 104-5°C $(\alpha)_D$ -24° Anal: $C_{31}H_{46}O$ C: 85.26 H: 11.08 found C: 85.26 H: 10.91	mp. 118-9°C $(\alpha)_D$ -32° $C_{30}H_{44}O$ C: 85.65 H: 10.54 found C: 85.91 H: 10.37

EXPERIMENTAL PART

3β-Methoxy-5-cholen-24-ol tosylate (I)

A solution of 3β-methoxy-5-cholen-24-ol[4] (1g) in 16 ml dry pyridine was cooled to 0°C and 1.3 g p-toluene sulfonyl chloride added slowly and with agitation under anhydrous conditions. After 1 hour, the mixture was precipitated on ice, extracted with ether, washed free of pyridine and crystallized from ether-methanol. Yield 95%, mp. 124-5°C $(\alpha)_D$ -35°, Analysis: $C_{32}H_{48}O_3S$ C:72.69 H:9.45
found C:72.31 H:9.22

Cholesteryl methyl ether (II: R_1 = isopropyl, R_2 = CH_3-)

To a suspension of 240 mg dry Mg in 10 ml dry THF was added slowly with stirring 1 ml 2-bromopropane. The mixture was agitated during 15 minutes and then cooled to 0°C. Slowly 1.4 ml of a solution of Li_2CuCl_4 (0.1 m mol in 1 ml THF)[2] was added. After completion of the addition of the complex, 200 mg (I) in 10 ml THF was added dropwise with agitation. After two hours at 0°C, the reaction mixture was left at room temperature over night. The solution was then acidified with 2N sulfuric acid, extracted with ether, and the product crystallized from metanol. Yield 78%, mp. 82-3°C, $(\alpha)_D$ - 45°(lit[3] mp. 84°C, $(\alpha)_D$ -46°).

Cholesterol: (II:R_1 = isopropyl, R_2 = H).

The above methyl ether was transformed into the acetate by the method of Ganem and Small[5], and the crude acetate hydrolysed to cholesterol.

To a solution of 250 mg cholesteryl methyl ether in 4 ml acetic anhydride and 4 ml ethyl acetate was added at room temperature and with stirring 16 mg anhydrous ferric chloride. After 1 hour of agitation the mixture was poured on ice, extracted with ether, the ether washed free of acid and evaporated. A solution of 100 mg of the crude acetate in 20 ml methanol and 5 ml 10% aeq. KOH was refluxed for 1 hour, diluted with water, acidified and the mixture extracted with ether. The ether was washed, dried and evaporated. The product was crystallized from ether methanol. Yield (w/w) from (I): 65%, mp. 144-5°, $(\alpha)_D$ -38° (lit[3] 148°, $(\alpha)_D$ -39°) identical in all respects with authentic cholesterol.

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