J. Serb. Chem. Soc. 60(12)1071-1073(1995)
JSCS-2009

UDC 547.923/.4:542.91
Original scientific paper

Novel and simple synthesis of 5β-cholestan-3-one*

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(Received 2 June 1995)

A two-step procedure for the synthesis of coprostanone is reported. The first step is the catalytic transfer hydrogenation of 4-cholesten-3-one over W2 Raney nickel in boiling isopropanol, which gives a mixture of 5β-cholestan-3α- and 3β-ols. In the second step the crude mixture of coprostanols is oxidized with Kiliani reagent to 5β-cholestan-3-one as the sole product, with overall yield 80%.

The classical hydrogenation of 3-oxo-4-ene and 3-oxo-1,4-diene steroids with gaseous hydrogen is a convenient route to 5β steroids.[1] Various catalysts have been studied: platinum black,[2] palladium oxide,[3] palladium hydroxide,[3,4] palladium black,[5] palladium on carbon,[6,7] and copper on alumina.[7] The best results were obtained with palladium black and substituted pyridines as solvents.[5]

The reduction of unsaturated bonds can be achieved with an organic molecule as hydrogen donor in the presence of a catalyst, a process defined by Braude and Linstead as 'Catalytic Transfer Hydrogenation' (CTH).[8] The CTH synthesis of coprostan-3-one from Δ^5- or Δ^4-cholesterol, accomplished with moderate yield, has attracted considerable attention.[9]

We now report an efficient synthesis of coprostanone *via* the catalytic transfer hydrogenation[10] of 4-cholesten-3-one over W2 Raney nickel in boiling isopropanol.

RESULTS AND DISCUSSION

The synthesis of 5β-cholest-3-one is outlined in Scheme 1. The catalytic transfer hydrogenation of 4-cholest-3-one(I) was performed over W2 Raney nickel in isopropanol that simultanously serves as solvent and hydrogen donor. After one hour of reflux the reduction was completed. The course of the reaction was followed by thin-layer chromatography. Conversion was broadly quantitative; TLC showed only one new, lower R_f, spot. ^{1}H-NMR spectrum showed a quintet at 3.55 ppm and a singlet at 4.02 ppm with integral ratio 1:0.3, and an absence of olefinic protons. Spectral data correspond to the mixture of 77% equatorial β-cholestan-3α-ol (II) and 23% 5β-

* Dedicated to the memory of the late Professor Aleksandar Leko.

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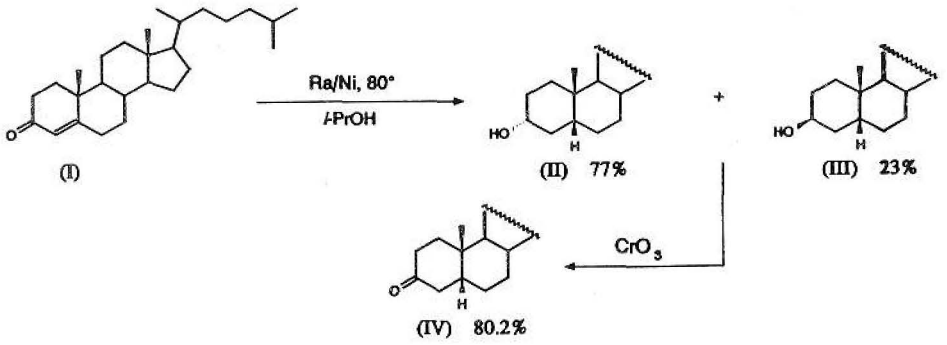
cholestan-3β-ol (III). Epimeric coprostanols (II + III) can only be separated with digitonin.[11,12] We confirmed their 5β-configuration by oxidation that gave 5β-cholestan-3-one (IV) as sole product.



Scheme 1.

In the second step the crude mixture of coprostanols was dissolved in acetone and oxidized by the dropwise addition of Kiliani reagent. After the work-up, 5β-cholestan-3-one (IV) was recrystallized from 90% ethanol. The overall yield was 80.2%.

The synthesis outlined in this work has at least two advantages. The high yield is comparable to that obtained with platinum black,[2] but using a much less expensive catalyst. (It should be mentioned that the catalyst in Ružička *et al.* paper (Ref. 2) is described vaguely as "ein alte Platinschwarz Präparat"). With an inexpensive catalyst – copper,[7] the yield is much lower. Our 80.2% yield is obtained by crystallization, whereas Ravasio *et al.*[7] got it by chromatography.

EXPERIMENTAL

W2 Raney nickel was prepared by the method of Mozingo *et al.*[13] After exhaustive washing, the water was decanted and the catalyst was stored under isopropanol in a refrigerator.

Kiliani reagent[14] was prepared by dissolving 60 g of sodium bichromate dihydrate in 270 ml of water and 80 g of concentrated sulfuric acid. The reagent contained 10% chromic acid.

A. Catalytic transfer hydrogenation of 4-cholesten-3-one (I). In a 10 ml flask, 300 mg of 4-cholesten-3-one (I) and 100 mg of W2 Raney nickel were suspended in 5 ml of isopropanol, and the reflux condenser was mounted. The vigorously stirred reaction mixture was refluxed for one hour. The reaction was monitored by thin-layer chromatography. Raney nickel (usually pyrophoric) was filtered over Celite in a stream of carbon dioxide and isopropanol was removed on the rotating vacuum evaporator. The product was 291 mg of the crude mixture of 5β-cholestan-3α-ol (II) and 5β-cholestan-3β-ol (III).

B. Oxidation of 5β-cholestan-3α-ol (II) and 5β-cholestan-3β-ol (III). The crude mixture of coprostanols (II) and (III) was dissolved in 25 ml of acetone, 0.55 ml of Kiliani reagent was added dropwise during 5 minutes, and stirring continued for 20 minutes. The reaction mixture was evaporated in a vacuum to a small volume (*ca.* 2 ml), diluted with 25 ml of water, and extracted with three portions of 25 ml of ether. The combined ethereal extract was washed with water, 5% sodium bicarbonate, again with water, and dried with anhydrous sodium sulphate. Ether was removed in a vacuum. Recrystallization from 90% ethanol afforded 242 mg of pure 5β-cholestan-3-one (IV); m.p. 60 °C (Ref. 15, 61-62 °C). Overall yield regarding the starting cholestenone (I) was 80.2%.

For all compounds correct m.p., IR, NMR, and elemental analysis were obtained.

ИЗВОД

НОВА И ЈЕДНОСТАВНА СИНТЕЗА 5β-ХОЛЕСТАН-3-ОНА

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Саопштен је једноставан поступак за синтезу копростанона у две фазе. Прва фаза је преносна хидрогенизација 4-холестен-3-она катализована W2 Raney-никлом у кључалом изопропанолу, која даје смешу 5β-холестан-3α- и 3β-ола. У другој фази се сирова смеша копростанола оксидује Kiliani-јевим реагенсом у 5β-холестан-3-он, који је једини производ, у укупном приносу од 80%.

(Примљено 2. јуна 1995)

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