Stereoselective and Regioselective Reduction of Steroid Ketones by Potassium Tri(*R,S*-s-butyl)borohydride

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Potassium tri(*R,S*-s-butyl)borohydride reduces 3-oxo-steroids of the 5α- and 5β-series to the axial alcohol under conditions in which the 17- and 20-ketone groups remain unaffected.

Steroid 3-ketones are more reactive than 17- or 20-ketones; however, with most reducing agents, the differences in reactivity are not sufficient to allow clean reactions at the 3-position while a 17- or 20-ketone remains intact, thus necessitating a somewhat circuitous route[1] or the use of acidic conditions (towards the 3-axial alcohol)[2,3] in the preparation of 3-hydroxy-17- or 20-ketones. During a study of the reduction of steroid ketones by potassium tri(*R,S*-s-butyl)borohydride[4,5] (K-Selectride R, Aldrich) it was found that the use of limited amounts of the reducing agent and low temperature allowed selective reduction of the 3-ketone to the 3-axial alcohol leaving the 17- and 20-ketone groups untouched. The conditions generally employed were addition of K-Selectride (0.5 M in tetrahydrofuran; 20 μmol) to a solution of the steroid (20 μmol) in tetrahydrofuran (15 ml) under dry argon. The product was isolated by ethyl acetate–water extraction and washing. The $NaOH–H_2O_2$ work-up described by Contreras and Mendoza[6] in their reduction of

Table 1. Reduction of steroid ketones by K-Selectride in tetrahydrofuran.

Substrate	Reaction time/h	Reaction temp./°C	%3α-OH	%3β-OH	% Diol	% Conversion
5α-Androstane-3,17-dione	2	−75	100	0	0	63
	2	22	96	4	0	78
	4	22	93	7	0	84
	20	22	93	7	0	86
5β-Androstane-3,17-dione	3	−75	0	100	0	86
	2	22	0	100	0	19
	5	22	0	100	0	19
	20	22	0	100	0	26
	22[a]	22	0	90	10	98
	25[b]	22	2	74	24	100
5α-Pregnane-3,20-dione	2	−75	100	0	0	25
	70	22	100	0	0	19
5β-Pregnane-3,20-dione	2	22	0	100	0	73
	5	22	3	97	0	76
	20	22	3	97	0	85
	65[c]	22	0	0	3β,20β 85% 3α,20β 10% 3β,20α 5%	100
			%17α-OH	%17β-OH		
Estrone methylether	1	22	19	81		10
	5	22	17	83		18
	24	22	18	82		28
	3[a]	22	18	82		100
	2[c]	22	19	81		100

[a] 1 equiv. excess of K-Selectride. [b] 2 equiv. excess of K-Selectride. [c] 10 equiv. excess of K-Selectride.

5α- and 5β-cholestanone to the axial alcohols and by Fortunato and Ganem[7] in the reduction of cyclohexanones does not appear to be necessary, and may, indeed, cause epimerization at the 17-position in the 20-oxopregnane series, a disadvantage shared with the sodium chloroiridate–phosphite reduction method.[2] The products were identified and yields determined by t.l.c. and h.p.l.c.

As can be seen in Table 1, reductions of the 3-ketone group carried out at −70 °C gave less than 0.5% of the equatorial 3-alcohol, the major products being the 3-axial alcohol-17-ketone. The regioselectivity was maintained at room temperature but stereoselectivity of 3-reduction decreased. With excess of reagent, reduction of the 17- and 20-ketones also occurred. Since our interest was primarily in the ratio of products, and we were working on a relatively small scale, no attempt has yet been made to increase the yields. The exclusion of water is probably the most important factor in determining the overall yield.

It was hoped that potassium tri(*R*,*S*-s-butyl)borohydride might reduce the 17-ketone to the pseudo-axial 17α-alcohol; however reduction of estrone methyl ether gave an 8:2 ratio of 17β:17α-alcohols much like that produced by borohydride and other conventional reagents, but not by the rhodium-(−)-diop–diphenylsilane system.[8] The reduction of 20-oxopregnanes to give a ratio 20β:20α 95:5 is also unexceptional. The reducing agent used here is a racemic mixture. The direction and rate of reduction of the ketones with the separate *R*- and *S*-chiral reagents remains to be studied.

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