

Reversal of the Direction of Asymmetric Induction in the Borohydride Reduction of Two Propiophenone Derivatives Using a Polymer-bound Reagent

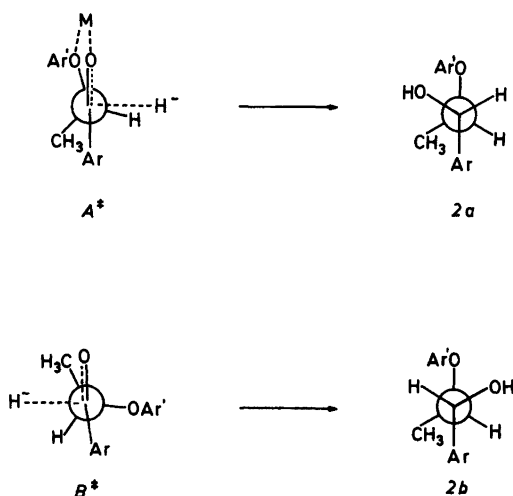
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In the course of a study on the synthesis of lignin model compounds, we have investigated the stereoselectivity of the borohydride reduction of **1** (Ar = 4-hydroxy-3-methoxyphenyl; Ar' = 2-methoxyphenyl).¹ The reaction normally yields a mixture of stereoisomers, with the *erythro* isomer **2a** predominating over the *threo* isomer **2b**.² We reduced the ketone at three temperatures. The composition of the mixture of diastereomers was determined with ¹H NMR at 100 MHz after acetylation. The signals most useful for integration were those from the methyl protons (δ 1.29 for *erythro* and δ 1.17 for *threo*³) and from the acetyl protons (δ 2.07 for *erythro* and δ 1.98 for *threo*). The results are shown in Table 1. The stereoselectivity of the reaction is quite high and there is an increase in the yield of *erythro* isomer at lower temperatures.⁴

A borohydride reducing agent immobilized on an anion exchange resin of the quaternary ammonium type has recently been described⁵ which offers the advantage of easy work-up. When this reagent was used for the reduction of **1** the reaction was slower and an almost complete reversal of the steric course of the reaction was observed (Table 1).

The formation of the *erythro* isomer in the sodium borohydride reduction of ketones with an oxygen substituent on the α -carbon has been explained⁶ by the formation of a 5-membered cyclic complex with the reducing agent (M in Scheme 1).

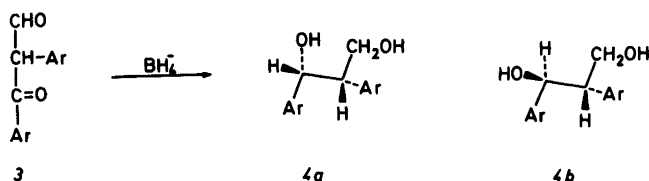
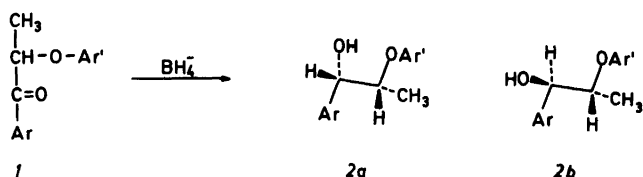


Scheme 1.

In Ref. 4 it is assumed that the complex is formed by the borohydride anion, the present results make it seem more probable that the cation is the complexing agent.⁶ This cyclic complex fixes the conformation of the ketone in a manner that makes an attack of the hydride ion on the least hindered side (transition state A*) lead to the formation of the *erythro* isomer **2a**. The increase in stereoselectivity at lower temperatures can be ascribed to an increase in the stability of this complex. The preferred formation of the *threo* isomer with the polymer-bound reagent indicates that the formation of a similar complex is prevented by the lack of coordinating ability of the reagent. In the absence of complex formation the preferred conformation of the transition state may be B* with maximal separation between the incoming nucleophile and the electronegative α -substituent.⁷ A less pronounced change in the asymmetric induction was

Table 1. Yields of diastereomeric products in the borohydride reductions of **1** and **3**.

Ketone	Reducing agent	Temp./°C	<i>erythro</i> (2a or 4a)/%	<i>threo</i> (2b or 4b)/%
1	NaBH ₄ /EtOH	6	89	11
1	NaBH ₄ /EtOH	20	86	14
1	NaBH ₄ /EtOH	78	81	19
1	Polymer/EtOH	20	28	72
3	NaBH ₄ /EtOH	20	Quant.	Trace
3	Polymer/EtOH	20	60	40



observed in the reduction of 3 where sodium borohydride reduction gives almost exclusively the *erythro* (*S,R+R,S*) isomer 4a.⁸ The polymer-bound reagent gave in this case a mixture of 60% 4a and 40% *threo* (*S,S+R,R*) isomer 4b (determined by integration of the benzylic proton signals in ¹H 4 with the aid of data from Ref. 9).

The present results indicate that, owing to a reduced ability for complex formation, the polymer-bound borohydride reagent does not possess greater selectivity than sodium borohydride in reductions of ketones having polar substituents.

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