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THE STEREOCHEMICAL COURSE OF EPOXIDE RING OPENING BY ALLYLIC GRIGNARD REAGENTS

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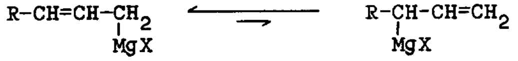
Unsymmetrical allylic Grignard reagents I are thought to consist mainly of the primary isomer Ia (1, 2, 3), in mobile equilibrium with a small proportion of the secondary isomer

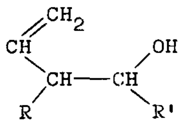


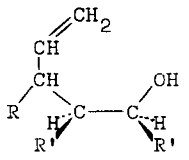
$$\text{R-CH=CH-}\underset{\substack{|\\ \text{MgX}}}{\text{CH}_2} \leftrightharpoons \text{R-}\underset{\substack{|\\ \text{MgX}}}{\text{CH}}\text{-CH=CH}_2$$

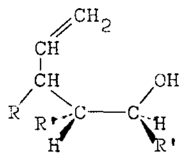
Ia Ib

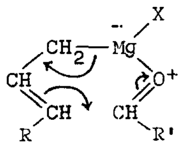
Ib (3). They are much more reactive than their saturated counterparts, and with most electrophilic substrates they afford rearranged products exclusively, e.g., branched alcohols II are formed from aldehydes (4, 5) and branched alcohols III (R' = H) are formed from ethylene oxide (6, 7).

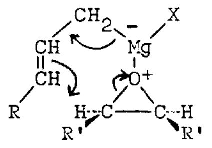
Although other possibilities have been considered (4, 5) to account for the special behaviour exhibited by these allylic reagents, it is generally assumed that their reactions involve the predominant, primary, isomer Ia, and proceed *via*


II


IIIe


IIIt


A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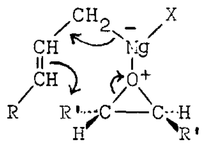
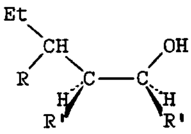
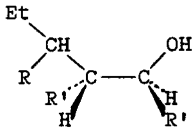

C

cyclic six-membered transition states such as A and B or C (7, 8, 9). A corollary of this cyclic S_Ei' mechanism is that epoxide ring opening by allylic Grignard reagents should be stereospecific and lead to *retention* of configuration at the epoxide carbon atom; in other words, if these reactions proceed *via* cyclic transition states (cf.B and C), *cis* epoxides should lead stereospecifically to *erythro* (or *cis*) alcohols IIIe, and *trans* epoxides to *threo* (or *trans*) alcohols IIIt. The work described below was undertaken in order to test this corollary.

Allyl (I, R = H) and pentenyl (I, R = Et) magnesium bromides were treated with dioxane and the resulting, halide-free, reagents were allowed to react in ether with epoxycyclohexane, *cis* epoxybutane, and *trans* epoxybutane. The resulting unsaturated alcohols III [R = H and Et; R'R' = $(CH_2)_4$ and R' = Me], isolated in good yield, were hydrogenated to the corresponding saturated alcohols IV; this eliminates the "extra" asymmetric centre which is present in the unsaturated compounds III (R = Et).



IVe



IVt

Gas chromatographic (GC) analysis of the alcohols III (R' = Me) and IV [R'R' = $(CH_2)_4$], under conditions under which their various stereoisomers could be cleanly separated (10), showed that the epoxide ring opening with halide-free reagents* was stereospecific (>99%) in all six cases.

Comparison (GC and IR) of the saturated alcohols IV, obtained by hydrogenation, with samples of the alcohols IVe and IVt [R = H and Et; R'R' = $(CH_2)_4$ and R' = Me] of established configuration (see below) showed that the cis epoxides had led stereospecifically to the threo (or trans) alcohols IIIt, and the trans epoxide to the erythro alcohols IIIe; in other words, all six reactions proceeded with inversion of configuration at the epoxide carbon atom.

The diastereoisomeric alcohols IVe and IVt were prepared as

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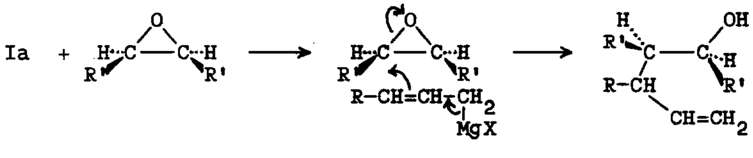
* The reactions are not entirely stereospecific when the reagent contains magnesium bromide. Thus, the reaction between allylmagnesium bromide and cis epoxybutane afforded the threo alcohol IIIt (R = H, R' = Me), GC analysis of which showed peaks having the retention times of the erythro isomer IIIe (R = H, R' = Me) (2%) and of allyl ethyl methyl carbinol (2%).

follows:

(a) Propyl series (R = H).- Erythro (IVe, R = H, R' = Me) and threo (IVt, R = H, R' = Me) 3-methyl 2-hexanol and trans 2-propyl cyclohexanol [IVt, R = H, R'R' = $(CH_2)_4$] were made stereospecifically (5, 11) from dipropylmagnesium and trans epoxybutane, cis epoxybutane and epoxycyclohexane, respectively. Cis 2-propyl cyclohexanol [IVe, R = H, R'R' = $(CH_2)_4$] was isolated (GC) as the minor product of the lithium aluminium hydride reduction of 2-propyl cyclohexanone.

(b) 3-Pentyl series (R = Et).- The reaction between di-3-pentyl magnesium and the same epoxides afforded none of the expected alcohols IV (R = Et), so trans 2-(3-pentyl) cyclohexanol [IVt, R = Et, R'R' = $(CH_2)_4$] was made stereospecifically by the hydroboration method (12) from 1-(3-pentyl) cyclohexene; this alcohol was oxidised to 2-(3-pentyl) cyclohexanone, the reduction of which by lithium aluminium hydride afforded (as the minor component) the cis isomer [IVe, R = Et, R'R' = $(CH_2)_4$]. The diastereoisomeric alcohols IVe and IVt (R = Et, R' = Me), obtained by hydrogenation from the unsaturated alcohols IIIe and IIIt, were oxidised to the same ketone (3-methyl 4-ethyl 2-hexanone); this was then reduced back with lithium aluminium hydride to a mixture of IVe and IVt (R = Et, R' = Me). Configurations were assigned to these alcohols on the basis of Cram's rule (13), according to which the major constituent of the mixture is the threo isomer IVt.

The fact that epoxide ring opening by allylic Grignard reagents occurs stereospecifically with inversion of configuration at the epoxide carbon atom means that a cyclic six-membered transition state (cf. B and C) cannot be involved. We suggest that the mechanism of this reaction is S_N2 with respect to the epoxide and S_E2' with respect to the primary isomer Ia of the Grignard reagent; this is depicted in the following scheme for the case of a <u>cis</u> epoxide:



<u>cis</u> D IIIt

A transition state such as D accounts most economically for the properties of allylic Grignard reagents:

(a) It predicts inversion of configuration at the epoxide carbon atom, and the formation of branched alcohols (<u>e</u>.<u>g</u>.III, R = Et)*, as observed.

(b) It is consistent with the fact that the reactivities, versus epoxycyclohexane, of primary (allyl) and secondary (αγ-dimethylallyl) Grignard reagents are very similar in competitive reactions (14); this observation indicates that we are not dealing with an S_E2 mechanism (4, 5, 15) involving the secondary isomer Ib, which is perhaps present in minor amounts in mobile equilibrium with the primary isomer Ia (3).

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* Not more than 3% of the straight-chain alcohol [<u>trans</u> 2-(Δ^2-pentenyl)cyclohexanol] is formed in the reaction between the pentenyl reagent (I, R = Et) and epoxycyclohexane.

(c) It is also consistent with the fact that allylic Grignard reagents, like a number of other allylic organometallics (16), are far more reactive than the corresponding saturated reagents*. The latter probably react by an S_E2 mechanism (with respect to the reagent) and, as has already been pointed out (16), this involves a transition state in which there are large repulsive forces between the entering electrophilic substrate and the leaving metal group; these repulsive forces are absent in an S_E2' transition state (cf. D), since the substrate and the metal group are not bound to the same carbon atom.

Evidence is accumulating in favour of an S_E2' reaction path for allylic organometallics (16), and it may well be that allylic Grignard reagents generally react by this mechanism, which entails a smaller loss of entropy in the transition state than the currently accepted cyclic S_Ei' mechanism.**

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* The reaction of cis epoxybutane with diallyl magnesium is finished in seconds under conditions under which the reaction with dipropyl magnesium requires hours.

** It has already been pointed out that the stereochemical course of the reaction between unsymmetrical allylic Grignard reagents and aldehydes is difficult to reconcile with a cyclic S_Ei' mechanism (5, 15, 17).

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