Tetrahedron Letters No. 7, pp 571 - 574, 1974. Pergamon Press. Printed in Great Britain.

# STERIC COURSE OF THE ADDITION OF NUCLEOPHILES TO 2-PHENYL-1,3-DIOXAN-5-ONE

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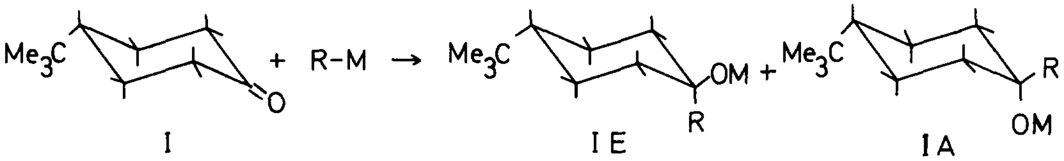
(Received in UK 1 November 1973; accepted for publication 11 January 1974)

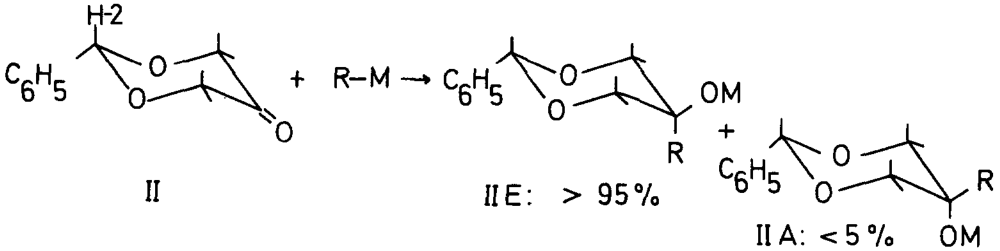
Six-membered ring ketones such as 4-tert-butyl-cyclohexanone, I, are attacked by nucleophiles (e.g., Grignard reagents or metal hydrides) from two different sites giving rise to products E with an equatorial OH group, and A with an axial OH group. The ratio of the amounts of E and A as well as the rate constants [1, 2] have recently been attributed to the operation of two factors:



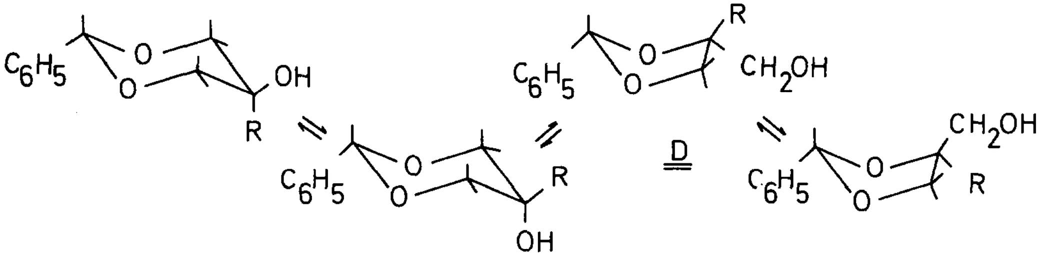
I IE IA

1) Axial attack (formation of E) is sterically hindered by the axial protons on C-3 and -5 (Steric Approach Control [3, 4]). 2) Equatorial attack (giving A) is sterically almost unhindered [5] but limited due to eclipsing effects [6] (Torsional Strain) between the forming R-C-1 bond and the axial H-C-2 and H-C-6 bonds. The steric course of the addition is determined by the competition of these two effects. If R is small (e.g., $H^-$), steric approach control is of little influence and E forms predominantly. If R is large (e.g., alkyl), then in the case of I the steric factor is slightly more important than the eclipsing factor and more A than E forms.

This paper reports the addition of Grignard reagents and LiAlH$_4$ 7) to the carbonyl group of 2-phenyl-1,3-dioxan-5-one, II 8). The results are given in the Table together with data from the literature for the corresponding reactions of I 1, 12). The reaction mixtures were analysed by proton magnetic resonance 9) in CCl$_4$ solution integrating the signals of the H-2 protons 10). These signals are well separated and can easily be assigned through comparison with the spectra of the pure compounds 11).



The dioxanone, II, reacts with Grignard reagents and LiAlH$_4$ almost exclusively through axial attack. With increasing size of R, reduction to the equatorial alcohol, II E (R=H) competes with addition. In the evolving gases during the reactions, ethylene, isopropylene, tert-butane + iso-butylene, depending on the Grignard reagent used, have been identified by NMR. The dioxolanes and axial alcohols, II A, are in our opinion secondary products formed through equilibration of the corresponding II E compounds by excess Grignard reagent and during the work-up procedure. Thus, leaving the Grignard reaction several hours at room temperature or refluxing before quenching with aqueous NH$_4$Cl results in considerable equilibration according to the scheme:



Alkyl magnesium bromides cause considerably more equilibration than do the iodides. While tert-butyl-MgCl is reported 12) to add to I giving I A only, it does not add to the dioxanone, II.

The results can be interpreted assuming that the axial free electron pairs of the $sp^3$ hybridized ring oxygens of II cause less steric hindrance to an axial attack of a nucleophile than do the axial protons on C-3 and -5 of the cyclohexanone, I, while equatorial attack is about equally hindered in both I and II by eclipsing effects. But other explanations can not be ruled out at this time: While a flexible conformation of I is energetically less favourable than the chair form, 13) the same is not necessarily true for the dioxanone, II, where boat or flexible forms should have smaller dipole moments than the chair form. If II reacts from a flexible form, equatorial attack might be prevented by steric repulsion of H-2. If II reacts from a chair conformation, complexation of the Mg in the Grignard reagent by the ring oxygens could be important in determining the steric course of the addition.

Table

| R-M a) | r/k b) | II: % Yield | %E(R=H) c) | %A(R=H) c) | D c) | %E d) | I:%E d) |
|---|---|---|---|---|---|---|---|
| $CH_3MgI$ | 2 | 94 | 0 | 0 | 0 | 98 | 45 |
| $CH_3CH_2MgI$ | 2 | 98 | 2 | 0 | 0 | 98 | 31 g) |
| $(CH_3)_2CH$-MgI | 3.5 | 98 | 10 | trace | 1 | 96 | 18 g) |
| $(CH_3)_3C$-MgCl | 3.5 | 90 | 90 | trace | trace | - e) | 0 f) |
| $LiAlH_4$ | 1.5 | 99 | 94 | 6 | 0 | - | 91 |

a) Solvent, diethylether. Reactions were carried out at room temperature except for the $LiALH_4$ reduction, which was at 0°.

b) Moles reagent to one mole of ketone.

c) Dioxolanes. Normalized: resulting mixture of all compounds = 100 %.

d) Normalized: % E + % A = 100 %.

e) No addition. The reaction mixture still contained 10 % of II.

f) About 1/3 reduction to the equatorial alcohol and 2/3 addition to I A 12).

g) The alkyl bromide was used.

Acknowledgement: This work was supported by Stiftung Volkswagenwerk, Fonds der Chemischen Industrie and Deutsche Forschungsgemeinschaft.

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