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THE REACTION BETWEEN KETONES AND T-BUTYLALLYL MAGNESIUM BROMIDE. A SENSITIVE MEASURE OF STERIC HINDRANCE IN THE NEIGHBOURHOOD OF THE CARBONYL GROUP.

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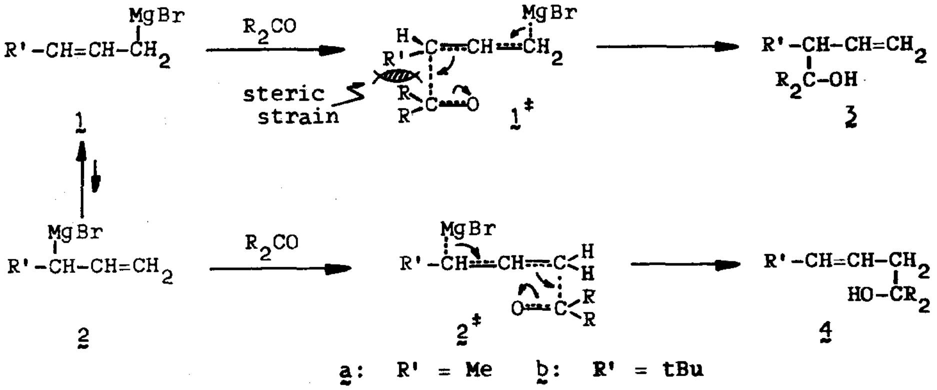
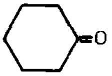
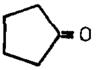
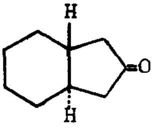
Unless they are overwhelmingly large, steric effects are often difficult to disentangle from other factors which influence reactivity (angle and torsional strain, polar effects, etc.).[1] We report that the ratio of products (4b/3b), formed in the reaction between t-butylallyl magnesium bromide (1b-2b) and various ketones, is extremely sensitive to the steric environment of the carbonyl group, and constitutes a useful measure of the effective ("kinetic") bulk of the groups R in relatively unhindered ketones R_2CO.



As we have recently pointed out,[2] the abundant experimental data now available lead to the conclusion that allylic Grignard reagents react with carbonyl compounds via a non-cyclic S_E2' rearrangement mechanism. In the case of unsymmetrical reagents ($1 \rightleftharpoons 2$), there are two possible isomeric S_E2' transition states, $1^{\ddagger}$ and $2^{\ddagger}$, leading to the isomeric carbinols 3 and 4. Using the same Grignard reagent, any variation in the product ratio 4/3 on going from one ketone R_2CO to another is expected to reflect only the difference between the effective bulks of the groups R: the bulkier R, the greater the steric strain in the transition state $\mathbf{1}^{\ddagger}$, and hence the greater the ratio **4**/**3** (see scheme). All the other differences between the two ketones should have about the *same* effect on the energies of the two transition states, and hence cancel; for example, making R more electron-withdrawing without changing its bulk should favour both transition states to about the same extent, and therefore leave the ratio **4**/**3** essentially unchanged.

The only unsymmetrical allylic Grignard reagent whose structure and reactions have been extensively studied is butenyl magnesium bromide. This reagent consists mainly of the crotyl isomer **1a**,[3] in mobile equilibrium with a very small proportion of the α-methallyl isomer **2a**.[4] The position of this equilibrium is such that, with relatively unhindered carbonyl compounds (*e.g.*, aldehydes,[5] acetone,[6] diethyl ketone, cyclopentanone, 4-t-butylcyclohexanone), the sole detectable products are the α-methallyl carbinols **3a** (**4a**/**3a** < 0.01). It is only with relatively hindered ketones that steric strain in the transition state $\mathbf{1a}^{\ddagger}$ becomes large enough for crotyl carbinols **4a** to be formed concurrently; thus, with di-isopropyl ketone the product ratio **4a**/**3a** (R = iPr) is 0.5,[7,8] and with di-t-butyl ketone the crotyl carbinol **4a** (R = tBu) predominates.[7,9] Butenyl magnesium bromide therefore only gives experimentally observable variations in product ratios (**4a**/**3a**) with a limited spectrum of ketones having rather bulky R-groups.

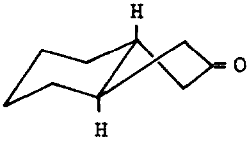
This spectrum can, however, be shifted towards relatively unhindered ketones by using t-butylallyl magnesium bromide (**1b**-**2b**)[10] instead of butenyl magnesium bromide (**1a**-**2a**). Steric strain in the transition state $\mathbf{1b}^{\ddagger}$ is increased to such an extent that even acetone now leads predominantly to the γ-t-butylallyl carbinol **4b** (R = Me),[11] and di-isopropyl ketone affords **4b** (R = iPr) exclusively.[12] The product ratios (**4b**/**3b**) obtained from various ketones were as follows:[13,14]

$(CD_3)_2CO$	$(CH_3)_2CO$	Et_2CO	iPr_2CO			
3.1	3.4	8	> 100	3	65	50

Two points warrant special comment:

(a) *Deuterium isotope effect*.- The decrease in product ratio on going from acetone to hexadeuteroacetone is in harmony with the view[15] that secondary deuterium isotope effects are steric in origin, CD_3 being less bulky than CH_3. The magnitude of the effect (1.107 ± 0.021)[16] emphasises the sensitivity of the product ratio to minute variations in the effective bulk of R.

(b) *Cyclopentanone*.- It is generally assumed that the relative reactivities of ring compounds are largely determined by the net variations in ring strain (I-strain) accompanying the reaction.[17] In five-membered rings, these variations are thought to arise essentially from differences in torsional strain between the ground state and the transition state. Such differences in torsional strain are expected to have essentially the same effect (unfavourable) on both the isomeric transition states **1b**‡ and **2b**‡ [$R_2 = (CH_2)_4$], and hence to have no more than a negligible effect on the product ratio **4b**/**3b**. It was therefore surprising to find a product ratio (65) indicating considerable steric strain in the transition state **1b**‡ involving cyclopentanone. The fact that *trans*-2-hydrindanone **5**, which is rigid, also gives a large product ratio (50) suggests that cyclopentanone reacts with nucleophiles via a transition state **6**‡ having a "half-chair" conformation, and that the steric strain arises from a gauche interaction (shown) between the bulky reagent and a methylene group. Although steric strain would be relieved in an "envelope" transition state such as **7**‡, this would only be at the expense of increased torsional strain.



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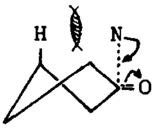
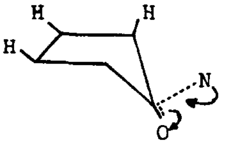


6‡



7‡

In conclusion, it is apparent that, in the reaction between the Grignard reagent **1b**-**2b** and ketones, quite subtle variations in the steric environment of the carbonyl group give rise to perceptible, and sometimes startling, variations in the product ratios **4b**/**3b**. An application of this reaction as a test for steric hindrance in the neighbourhood of the carbonyl group in 4-t-butylcyclohexanone is discussed in the accompanying paper.[18]

Footnotes

1. For a recent review, see J. Shorter, *Quart.Rev.*, **24**, 433 (1970).
2. H.Felkin and C.Frajerman, *Tetrahedron Letters*, 1045 (1970); H.Felkin, Y.Gault, and G.Roussi, *Tetrahedron*, **26**, 3761 (1970).
3. M.Gaudemar, *Bull.Soc.Chim.Fr.*, 1475 (1958).
4. J.E.Nordlander, W.G.Young, and J.D.Roberts, *J.Amer.Chem.Soc.*, **83**, 494 (1961).

5. Ou Kiun Houo, *Ann.Chim.(France)*, 13, 175 (1940).
6. J.D.Roberts and W.G.Young, *J.Amer.Chem.Soc.*, 67, 148 (1945).
7. R.A.Benkeser, W.G.Young, W.E.Broxterman, D.A.Jones, and S.J.Piaseczynski, *J.Amer.Chem.Soc.*, 91, 132 (1969).
8. See also W.G.Young and J.D.Roberts, *J.Amer.Chem.Soc.*, 67, 319 (1945), and B.Gross and C.Prévost, *Bull.Soc.Chim.Fr.*, 3610 (1967).
9. See also footnote 6 in R.A.Benkeser and W.E.Broxterman, *J.Amer.Chem.Soc.*, 91, 5162 (1969).
10. Prepared in 60% yield from a mixture of the corresponding bromides, bp$_{34}$ 65-68° [Lit., bp$_{28}$ 61.5-62°: P.B.D. de la Mare, E.D.Hughes, P.C.Merriman, L.Pichat and C.A.Vernon, J.Chem.Soc., 2563 (1958)].
11. With acetaldehyde, however, **4b**/**3b** < 0.01: the sole detectable products were the α-t-butylallyl carbinols **3b** (CR_2 = CHMe, 2 diastereoisomers).
12. This reaction was also reported recently by R.A.Benkeser and D.A.Jones, *Abstracts of Papers*, A.C.S. 156th National Meeting, ORGN136 (1968); D.A.Jones, *Dissert.Abstracts*, 29, 2810B (1969).
13. In all cases, the γ-t-butylallyl carbinols **4b** were predominantly *trans* (*trans*/*cis* > 20).
14. The reactions were performed in ether at 0° and were followed by immediate work-up. Gas chromatography was used to determine the product ratios and to isolate the products. Except for *cis*-**4b** ($R = CD_3$), which was identified by its retention time, and *cis*-**4b** (R = iPr), which was not obtained pure, all the carbinols **3b** and **4b** explicitly or implicitly mentioned were isolated and had i.r. and mass spectra consistent with the structures assigned to them; the structures of those formed in >10% yield were confirmed by n.m.r. Two of the products crystallised and gave satisfactory CH analyses: *trans*-**4b** [$R_2 = (CH_2)_5$], mp 37-38°, and *trans*-**4b** [$R_2 = (CH_2)_4$], mp 34.5-35°. The α-t-butylallyl carbinol **3b** [$R_2 = (CH_2)_5$] was recovered unchanged after refluxing for one month in ether with an excess of Grignard reagent (**1b**-**2b**); these reactions are therefore essentially irreversible (cf. ref. 9).
15. Inter al., G.H.Cooper and J.McKenna, *Chem.Commun.*, 734 (1966); H.C.Brown, M.E.Azzaro, J.G.Koelling, and G.J.McDonald, *J.Amer.Chem.Soc.*, 88, 2520 (1966).
16. 99% confidence limits (from statistical analysis of three independent pairs of experiments involving a total of 74 GC analyses).
17. Review: J.Sicher, *Progress in Stereochemistry*, 3, 202 (1962).
18. M.Chérest and H.Felkin, *Tetrahedron Letters*, see following paper.