Tetrahedron Letters No. 13, pp. 1045-1048, 1970. Pergamon Press. Printed in Great Britain.

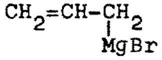
COMPETITIVE RATE STUDIES FOR SOME REACTIONS INVOLVING THE ALLYL, BUTENYL, αγ-DIMETHYLALLYL, AND PROPYL GRIGNARD REAGENTS. THE MECHANISM OF THE REACTIONS OF ALLYLIC GRIGNARD REAGENTS WITH ELECTROPHILIC SUBSTRATES.

Hugh Felkin and Claude Frajerman

Institut de Chimie des Substances Naturelles, C.N.R.S.,
91-Gif-sur-Yvette, France.

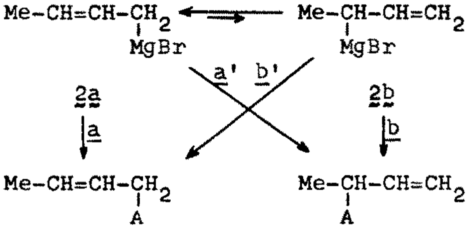
(Received in UK 2 February 1970; accepted for publication 12 February 1970)

Butenyl magnesium bromide 2ab, the prototype of unsymmetrical allylic Grignard reagents, reacts with unhindered electrophilic substrates A-B, such as carbonyl compounds[1] and epoxides,[2,3] to afford branched products 4b. It is



$CH_2=CH-CH_2MgBr$

1

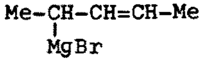


$Me-CH=CH-CH_2MgBr \rightleftharpoons Me-CH(MgBr)-CH=CH_2$

2a 2b

$Me-CH=CH-CH_2A$ $Me-CH(A)-CH=CH_2$

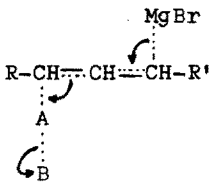
4a 4b



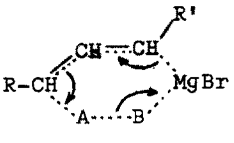
$Me-CH(MgBr)-CH=CH-Me$

3

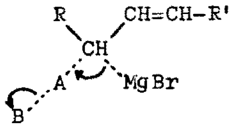
generally assumed that these branched products are formed, with concomitant rearrangement, from the predominant, primary, isomer 2a of the reagent (route a'), and not, as has sometimes been suggested,[4] via a direct displacement



S_E2'



S_Ei'



S_E2

(S_E2; R = Me, R' = H) from the secondary isomer 2b (route b). We report competitive rate studies which show that this is indeed so, but which strongly suggest that, contrary to prevailing opinion,[5] this rearrangement (route a') never involves a cyclic transition state ($S_E i'$; R = Me, R' = H).

If the reaction occurred via direct S_E2 displacements (routes a and b), the reactivity ratio between the two isomers **2a** and **2b** would have to be considerable (k_b/k_a > 600), since the ratio (**2a**/**2b**) of the two isomers in the butenyl Grignard reagent is at least 6,[6] and the ratio of the products (**4b**/**4a**), in the case of unhindered substrates such as acetone and epoxycyclohexane, is at least 100 (the linear isomer **4a** cannot be detected). This reactivity ratio cannot be measured directly, since the two isomers **2a** and **2b** are rapidly interconverted.[6b] We have therefore used allyl magnesium bromide **1** and αγ-dimethylallyl magnesium bromide **3** as models[6a] for the primary **2a** and secondary **2b** isomers of butenyl magnesium bromide, respectively, and we have determined the relative reactivities of these three reagents, and of propyl magnesium bromide, towards two electrophilic substrates, acetone and epoxycyclohexane.

The competitive reactivity ratios shown in the Table were obtained by slowly adding the substrate to a large excess of an equimolar mixture of a pair of Grignard reagents, and determining the product ratio by gas chromatography, the products being identified by their retention times. With epoxycyclohexane, which reacts relatively slowly, reproducible and internally consistent (0.14/0.34 ≈ 0.39) results could be obtained simply by adding an ethereal solution of the epoxide dropwise to a stirred mixture of two Grignard reagents. The rate of reaction of acetone, however, appears to be greater than the rate of mixing when dropwise addition is used,[7] since this technique led to an allyl/propyl product ratio of only 7, whereas the allyl/propyl product ratio was 700 when acetone vapour (~ 1 μg/min), mixed with nitrogen (~ 2 ml/min), was slowly admitted above the surface of a stirred mixture of the two Grignard reagents. Although this vapour addition technique overcomes mixing limitations, it leads to product ratios (see Table) which are only reproducible to within a factor of about two, and whose internal consistency is far from perfect (1/0.7 ≠ 4). Nevertheless, it is quite clear that the secondary

TABLE

Competitive reactivity ratios for various pairs of Grignard reagents versus epoxycyclohexane (dropwise addition) and acetone (vapour addition).

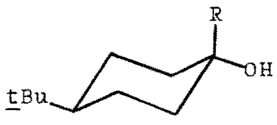
Grignard reagents	epoxycyclohexane	acetone
allyl/propyl	820	700
butenyl/allyl	0.34	0.7
αγ-dimethylallyl/allyl	0.14	1
αγ-dimethylallyl/butenyl	0.39	4

reagent 3 does not react faster than the primary reagent 1 with either acetone or epoxycyclohexane. It follows that the secondary isomer 2b of the butenyl reagent cannot conceivably be over 600 times more reactive than the primary isomer 2a, and that the formation of branched products 4b from both acetone and epoxycyclohexane must therefore be occurring, with rearrangement, from the primary isomer 2a (route a'), and not via a direct displacement (S_E2) from the secondary isomer 2b (route b). Furthermore, the fact that the reactivities of the three allylic Grignard reagents 1, 2 and 3 differ by less than an order of magnitude indicates that the two symmetrical reagents 1 and 3 must also be reacting with rearrangement, and not via a direct S_E2 displacement.

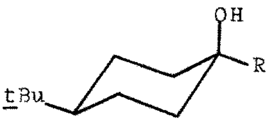
Both acetone and epoxycyclohexane react about three orders of magnitude faster with allyl magnesium bromide than with the corresponding primary alkyl Grignard reagent, propyl magnesium bromide (see Table); they both afford branched products 4b with butenyl magnesium bromide ; and they both show the same "cis-preference" in their reactions with αγ-dimethylallyl magnesium bromide.[8] This identity in behaviour leads inescapably to the conclusion that they both react with allylic Grignard reagents by an identical mechanism. And since the epoxide reaction cannot involve a cyclic S_Ei' transition state,[3] the same must be true for acetone, and hence for carbonyl compounds in general.[9]

Unlike the S_E2 and S_Ei' mechanisms, a non-cyclic rearrangement mechanism[3,8] (S_E2'; R = Me, R' = H) is entirely consistent with all the facts outlined above, and we suggest that the branched products 4b are generally formed from the primary isomer 2a (route a') by this mechanism.

It has recently been suggested[5,10] that the straight-chain products 4a, which are formed when steric overcrowding (involving R and A-B) is severe in the transition state leading to the branched products 4b (route a'), arise via a direct S_E2 displacement from the primary isomer 2a (route a). Evidence that this is not so, and that these straight-chain products are also formed by an S_E2' rearrangement mechanism (route b'), is provided by the preferential formation of the axial straight-chain epimer 5a in the reaction between t-butylcyclohexanone and t-butylallyl magnesium bromide (2ab, Me replaced by tBu).[11a] The ratio of epimers (5a/6a = 1.2) is typical of an S_E2' (R = H) process (with



5



6

a: R = CH_2-CH=CH-tBu
b: R = CH_2-CH=CH_2
c: R = CH_2-CH_2-CH_3

allyl magnesium bromide, 5b/6b = 1.06),[11b] and quite different from the ratio obtained in an S_E2 process (with propyl magnesium bromide, 5c/6c = 0.35).[11b] Moreover, the "cis-preference" observed in the reactions of butenyl magnesium bromide with hindered ketones[5,10] can be readily explained[8] if the products 4a arise by an S_E2' mechanism.

One may ask why allylic Grignard reagents, and allylic organometallics in general,[12] prefer to react via a non-cyclic S_E2' transition state rather than via an aesthetically more satisfying cyclic S_Ei' transition state. The answer to this question may have to do with conservation of orbital symmetry, since it has been suggested[13] that a concerted electrophilic substitution occurring with rearrangement must be an antarafacial process. This requirement can be met in an S_E2' transition state, whereas an S_Ei' transition state necessarily implies a suprafacial process.

We thank Professors R.Corriu, C.K.Ingold and P.S.Skell for helpful comments and suggestions. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Footnotes

1. Ou Kiun-Houo, Ann.Chim.(France), 13, 175 (1940); J.D.Roberts and W.G. Young, J.Amer.Chem.Soc., 67, 148 (1945).
2. L.S.Wu, R.A.Finnegan, and K.W.Greenlee, Abstracts of Papers, ACS Meeting, September 1962, p. 7Q; M.Andrac, F.Gaudemar, M.Gaudemar, B.Gross, L.Miginiac, P.Miginiac, and C.Prévost, Bull.Soc.chim., 1385 (1963).
3. H.Felkin and G.Roussi, Tetrahedron Letters, 4153 (1965).
4. See Y.Gault and H.Felkin, Bull.Soc.chim., 1342 (1960).
5. R.A.Benkeser, W.G.Young, W.E.Broxterman, D.A.Jones, and S.J.Piaseczynski, J.Amer.Chem.Soc., 91, 132 (1969).
6. (a) M.Gaudemar, Bull.Soc.chim., 1475 (1958); (b) J.E.Nordlander, W.G. Young, and J.D.Roberts, J.Amer.Chem.Soc., 83, 494 (1961).
7. Limitations due to the relative slowness of mixing in very fast competitive reactions have been discussed by W.S.Tolgyesi, Can.J.Chem., 43, 343 (1965).
8. H.Felkin, C.Frajerman, and Y.Gault, Chem.Commun., 75 (1966).
9. The steric course of the reaction between aldehydes and allylic Grignard reagents supports this conclusion; see ref.4 and H.Felkin, Y.Gault, and G.Roussi, paper submitted to Ann.Chim.(France).
10. B.Gross and C.Prévost, Bull.Soc.chim., 3610 (1967).
11. M.Chérest and H.Felkin, (a) unpublished observations; (b) Tetrahedron Letters, 2205 (1968).
12. M.Gielen and J.Nasielski, Ind.chim.Belge, 29, 767 (1964).
13. Nguyen Tronh Anh, Chem.Commun., 1089 (1968).