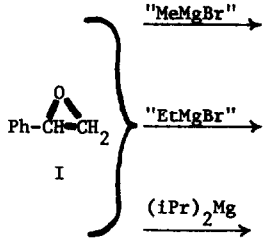
Tetrahedron Letters No.53, pp. 4635-4638, 1970. Pergamon Press. Printed in Great Britain.

THE REGIOSELECTIVITY AND STEREOSELECTIVITY OF THE REACTION OF STYRENE OXIDE AND DIALKYLMAGNESIUM REAGENTS*

J. D. Morrison, R. L. Atkins and J. E. Tomaszewski

Department of Chemistry, Parsons Hall
University of New Hampshire, Durham, N. H., 03824, U.S.A.
(Received in USA 9 October 1970; received in UK for publication 16 October 1970)

Grignard reagents and dialkylmagnesium compounds react differently with many epoxides. There is evidence which indicates that Grignard reagents usually promote more rearrangement than their less Lewis acidic dialkylmagnesium counterparts. For example, styrene oxide yields 1-phenyl-2-propanol and 1-phenyl-2-butanol when allowed to react with Grignard reagents from methyl bromide and ethyl bromide, respectively (1), whereas its reaction with diisopropylmagnesium produces mainly 3-methyl-2-phenyl-1-butanol (2). The first two reactions proceed via addition to an intermediate aldehyde complex resulting from a hydride shift, but the last reaction involves an apparent nucleophilic substitution of the alkyl group at the benzylic position.



I

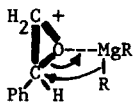
$PhCH_2CH(OH)Me$ II

$PhCH_2CH(OH)Et$ III

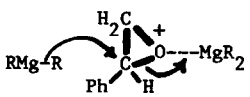
$PhCH(iPr)CH_2OH$ IV

(Only the major products are shown)

The benzylic attack pathway, which characterizes the principal result with most dialkylmagnesium reagents, poses a mechanistic question. One can envisage as reasonable mechanisms either an intramolecular transfer of an alkyl group in an epoxide complex, as represented in V, or an intermolecular transfer, as shown in VI. These alternatives are similar to those



V



VI

visualized by Ashby and Prather for the reaction of styrene oxide with electrophilic hydride transfer reagents (3).

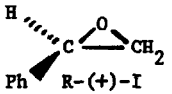
Using optically active styrene oxide as the substrate, and dialkylmagnesium reagents prepared by treatment of ethereal Grignard reagents with dioxane, we have determined that the introduction of an ethyl or isopropyl group occurs with about 80% inversion and 20% retention of

configuration at the benzylic carbon, i.e., about a 69% excess of inverted product over racemic product is produced. Therefore mechanistic alternative VI is more reasonable than V as a description of the primary mode of reaction since the latter should be characterized by net retention of configuration or racemization depending upon the extent to which epoxide opening and alkyl group substitution are concerted events.

The experiments upon which our conclusions are based are summarized in Table I. The following points should be noted: (a) In none of the reactions investigated was there any product arising from direct S_N2 attack at the primary carbon of the epoxide, i.e., no products having the general structure $PhCH(OH)CH_2R$. (b) Using a filtered, halide-free dialkylmagnesium reagent containing no suspended magnesium halide-dioxanate the yield of benzylic substitution product was greatly increased as compared to a reaction in the presence of dioxanate, e.g., a 95% versus a 50% yield of $PhCH(Et)CH_2OH$ ($R_2Mg = Et_2Mg$). In the presence of suspended dioxanate a significant portion of the product resulted from addition of Et_2Mg to the phenylacetaldehyde complex which results from a hydride shift. The percentage inversion at the benzylic position was also higher when filtered reagents were used. When the more acidic magnesium halide is not removed from the reaction by filtration of the dioxanate complex prior to addition of styrene oxide, it apparently competes with the R_2Mg for the basic oxygen of the epoxide and promotes formation of a more open benzylic carbonium ion which rearranges to a phenylacetaldehyde complex or goes to the benzylic substitution product with overall lower stereoselectivity. (c) Di-t-butylmagnesium in the presence of suspended magnesium chloride-dioxanate gave mainly (79%) 2-phenylethanol (IX) via reduction of (rather than addition to) the phenylacetaldehyde complex, and almost none (3%) of the benzylic addition product (VII) was produced. Filtered di-t-butylmagnesium, however, gave mainly (50%) addition at the benzylic carbon, and reduction of the hydride shift intermediate was greatly reduced (16%). The stereoselectivity of the di-t-butylmagnesium reaction was much lower than that observed for the ethyl and isopropyl reagents; only a 5.5% excess of inverted over racemic product was produced. The extensive racemization observed suggests to us that epoxide opening precedes the formation of the bond between the benzylic carbon and t-butyl group to a degree that permits the almost complete loss of configurational integrity by rotation about the C-1 to C-2 bond. However, in this case as in the other reactions examined one cannot exclude the competitive operation of mechanism V with retention and mechanism VI with inversion, the latter predominating, as a rationale of the experimental observations.

In addition to clarifying the mechanism this work provides support for the contention that the configuration of (+)-3-methyl-2-phenyl-1-butanol is S. The (-)-enantiomer was originally assigned an S configuration by Cervinka and Hub (4), but more recent work by Clark and Mosher (5) and Cervinka and Hub (6) has reversed this and other configurational assignments on the basis of what appear to be unequivocal chemical correlations. Our data are in agreement with the revised configurational assignment for IV [S-(+)] in the following way. The configuration of the product [(+)-$PhCH(Et)CH_2OH$] from reaction of the diethylmagnesium reagent

TABLE I



1) R_2Mg
2) H_2O

$PhCHRCH_2OH$ + $PhCH_2CH(OH)R$ + $PhCH_2CH_2OH$

	VII	VIII	IX
	Benzylic Substitution	Rearrangement with Addition	Rearrangement with Reduction

R	Product	% Yield[a], %e.e.[b], Configuration	Stereochemistry of VII Formation % Inversion	% Retention
Filtered Dialkylmagnesium Reagents:				
Et	VII	95%, 70% e.e., S-(+)	85	15
	VIII	4%, inactive		
t-Bu	VII	68%, 5.5% e.e., S-(-)	53	47
Dialkylmagnesium Reagents Containing Suspended $MgBr_2$-Dioxanate:				
Et[c]	VII	50%, 50% e.e., S-(+)	75	25
	VIII	30%, inactive		
i-Pr[c]	VII	48%, 63%, e.e., S-(+)	82	18
	VIII	20%, inactive		
i-Bu	VII	52%, α_D^{25}+2.38(neat), $[\alpha]_D^{26}$+4.25($CHCl_3$)[d]		
	VIII	23%, inactive		
	IX	4%, achiral compound		
t-Bu[e]	VII	3%, VII and VIII were not separated		
	VIII	18%, and no rotation data were taken.		
	IX	79%, achiral compound		

(a) Yields were determined by glpc analysis of undistilled reaction mixtures unless otherwise annotated. The difference between the sum of the yields of the reported products and 100% is due to the presence of unreacted starting material and minor by-products, some of which were not identified, but none of which were $PhCH(OH)CH_2R$. (b) %e.e. is the percent enantiomeric excess corrected for the %e.e. of the R-(+)-styrene oxide used. The latter ranged from 84 to 89% for the reactions reported here. (c) These yields are computed from glpc analysis following simple distillation of the ether soluble reaction products. (See also footnote a). (d) The maximum rotation is not known. (e) Suspended $MgCl_2$-dioxanate in this case.

with R-(+)-styrene is known (7) to be S; that of the di-t-butylmagnesium product [(-)PhCH(t-Bu)CH_2OH] is also S (5). It seems reasonable that Et_2Mg, t-Bu_2Mg and iPr_2Mg should give analogous stereochemical results (a net excess of inversion) with styrene oxide under the same conditions. Therefore, the product from the reaction of the diisopropylmagnesium reagent with R-(+)-styrene oxide should also be S.

Assuming that other R_2Mg reagents behave similarly, this general reaction offers an alternative to asymmetric transformation and optical correlation methods (see Ref. 5 for a summary) for determining the configuration of compounds of the type PhCH(R)CH_2X where these can be prepared from the chiral alcohol (X=OH) obtained from chiral styrene oxide and the appropriate R_2Mg reagent, or where an optically active compound (X≠OH) obtained in another manner can be converted to the alcohol. From a synthetic standpoint the commercial availability of both enantiomers of optically active mandelic acid from which the chiral styrene oxide was prepared (8) makes feasible the synthesis of both enantiomers of a 2-substituted-2-phenylethanol using this reaction. Related work is continuing with other chiral epoxides and other organometallics.

Acknowledgements: We thank the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. J.E.T. was an NSF Trainee for the period 1965-1969. R.L.A. was an NDEA Fellow, 1969-70. We thank Prof. H. S. Mosher for providing polarimetric data prior to its publication (5).

References

*The term regioselective (A. Hassner, J. Org. Chem., 33, 2684 [1968]) refers to the fact that there is preferential opening of the styrene oxide via displacement at the benzylic rather than terminal carbon. The reactions described in this paper are, in terms of these hypothetically competitive modes of ring opening, 100% regioselective, i.e., they may be said to be regiospecific. The term stereoselective refers to the stereochemistry of the benzylic displacement which occurs predominantly with inversion of configuration.

(1) (a) M. Tiffeneau and E. Fourneau, Compt. rend., 146, 697 (1908). (b) M. Tiffeneau and E. Fourneau, Chem. Zentr., 1, 1776 (1908).

(2) G. M. Whitesides and J. D. Roberts, J. Amer. Chem. Soc., 87, 4878 (1965), and this work. Many other examples of similar behavior can be cited; see J. E. Tomaszewski, Ph.D. Thesis, University of New Hampshire, 1970. References will be sent on request.

(3) E. C. Ashby and J. Prather, J. Amer. Chem. Soc., 88, 729 (1966).

(4) D. Cervinka and L. Hub, Coll. Czech. Chem. Commun., 33, 1911 (1968).

(5) D. R. Clark and H. S. Mosher, J. Org. Chem., 35, 1114 (1970).

(6) See footnote 21 in Ref. 5; also O. Cervinka and L. Hub, Coll. Czech. Chem. Commun., 35, 721 (1970).

(7) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson and H. S. Mosher, J. Org. Chem., 29, 37 (1964).

(8) The R-(+)-styrene oxide was prepared from R-(-)mandelic acid by the method of I. Tomoskozi, Tetrahedron, 19, 1969 (1963).