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# ASYMMETRIC SYNTHESIS. PART IV. THE STEREOSELECTIVITY OF GRIGNARD-CARBONYL REACTIONS IN SOLVENTS THAT CONTAIN CARBOHYDRATES

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It has been demonstrated (1,2,3,4) that chiral products can be formed in reactions between achiral Grignard reagents and aldehydes or ketones, in optically active solvents or when the solvent contains an optically active substance. Generally the stereoselectivity of such reactions is low and indeed the highest optical yield hitherto reported (3) is 17% [for the formation of 2-phenylbutan-2-ol from butan-2-one and $C_6H_5MgBr$ in (S)dimethoxybutane-benzene]. We have observed that in the presence of suitably substituted carbohydrates RMgX-R'COR" reactions can yield products with optical yields as high as 70%.

The availability of optically pure S(-)cyclohexylmethylphenylcarbinol ($[\alpha]_D$ - 20.6° in $CHCl_3$) prompted the study of its stereoselective formation by $MeMgX-C_6H_5COC_6H_{11}$, $C_6H_5MgX-CH_3COC_6H_{11}$, $C_6H_{11}MgX-CH_3COC_6H_5$ Grignard-ketone reactions. Surprisingly, the stereoselective formation of carbinols by only two of the three possible ketone-Grignard reactions appears to have been investigated previously. The reactions were carried out in ether and the carbohydrate was usually 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (I). The best optical yields were obtained when the ketone (1 mol) was added to a solution at room temperature of the glucofuranose derivative (I, 2 mol) in ether to which the Grignard reagent (3.5 mol) had been added previously. The products were purified by chromatographic techniques and the stereoselectivity of the addition reactions was measured polarimetrically. For comparison with previous investigations of this type the formation of 2-phenylbutan-2-ol by Grignard-ketone reactions and the formation of 1-phenylpropan-1-ol by Grignard-aldehyde reactions were also studied. The optical yields for the Grignard-carbonyl reactions in the presence of (I)

TABLE 1

Stereoselectivity of RMgX R'COR" Reactions in the Presence of 1,2:5,6-Di-O-Isopropylidene-α-D-glucofuranose (I)

| Reaction | RMgX | R'COR" | Product (% Yield) | | Specific Rotation° (Optical Yield %) | | Enantiomeric Proportions R : S |
|---|---|---|---|---|---|---|---|
| 1. | $CH_3MgI$ | $C_6H_5COC_6H_{11}$ | $C_6H_5C(OH)(CH_3)\ C_6H_{11}^{a}$ | (88) | + 13.35 | (65) | 82.5 : 17.5 |
| 1a. | $CH_3MgBr$ | $C_6H_5COC_6H_{11}$ | $C_6H_5C(OH)(CH_3)C_6H_{11}^{a}$ | (95) | + 14.3 | (70) | 85 : 15 |
| 2. | $C_6H_5MgBr$ | $C_6H_{11}COCH_3$ | $C_6H_5C(OH)(CH_3)C_6H_{11}^{a}$ | (60) | - 5.3 | (26) | 37 : 63 |
| 3. | $C_6H_{11}MgBr$ | $C_6H_5COCH_3$ | $C_6H_5C(OH)(CH_3)C_6H_{11}^{a}$ | (50) | - 5.8 | (28) | 36 : 64 |
| 4. | $C_2H_5MgBr$ | $C_6H_5COCH_3$ | $C_6H_5C(OH)(CH_3)C_2H_5^{b}$ | (45) | - 4.75 | (27) | 36.5 : 63.5 |
| 5. | $C_6H_5MgBr$ | $CH_3COC_2H_5$ | $C_6H_5C(OH)(CH_3)C_2H_5^{b}$ | (70) | - 1.8 | (10) | 45 : 55 |
| 6. | $CH_3MgBr$ | $C_6H_5COC_2H_5$ | $C_6H_5C(OH)(CH_3)C_2H_5^{b}$ | (70) | + 4.2° | (24) | 62 : 38 |
| 7. | $C_2H_5MgBr$ | $C_6H_5CHO$ | $C_6H_5CHOHC_2H_5^{b}$ | (81) | + 7 | (24) | 62 : 38 |
| 8. | $C_6H_5MgBr$ | $C_2H_5CHO$ | $C_6H_5CHOHC_2H_5^{b}$ | (60) | + 2.7 | (9) | 54.5 : 45.5 |

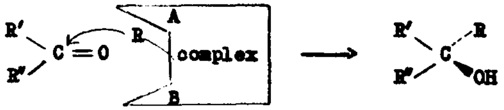
a Optically pure S cyclohexylmethylphenylcarbinol, ($[\alpha]_D$ - 20.6° in $CHCl_3$) was prepared by sequential reduction, toluene-p-sulphonation and reduction of S(+)2-cyclohexyl-2-hydroxy-2-phenylacetic acid (5).

b Information about the configuration and rotations of 2-phenylbutan-2-ol and 1-phenylpropan-1-ol is given in ref.1.

and listed in Table 1 were generally about 25 % but were much higher in favourable cases.

It is pertinent to comment first on the use of the glucofuranose derivative (I) in ether as the solvent medium for the addition reactions since this chiral medium is significantly different to those used in other investigations. Previously optically active ethers or benzene containing an optically active ether have been used and for the results reported, particularly where methylated alditols were used as the optically active ether (3), the degree of stereoselectivity of the addition reactions was low. The glucofuranose derivative (I) contains a free hydroxyl group which was first allowed to react with an equimolar quantity of Grignard reagent. Addition of a second equimolar quantity of Grignard reagent to the 3-OMg derivative of (I) formed a chiral Grignard-sugar complex, evidence in support of which was provided by rotational studies. It has been demonstrated that the rotation of chiral ethers in benzene is enhanced by complex formation with Grignard reagents but that usually the addition of achiral ethers to the mixture considerable reduces the rotational enhancement (6). When an equimolar quantity of MeMgI was added to (I) in the achiral ether, diethylether, the rotation changed from -6° to -3°. However addition of a second equimolar quantity of MeMgI caused the rotation to change to -30°. Essentially the same changes in rotation were observed with $C_6H_5MgBr$ and $C_6H_{11}MgBr$. Perhaps significantly the rotations of the 3-O-methyl and 3-O-benzyl ethers of (I) were not enhanced by addition of an equimolar quantity of Grignard reagent and optically inactive carbinols resulted from RMgX—R'COR" reactions in their presence. This evidence suggests that (I) forms a very strong complex with the Grignard reagent which is independent of the nature of the Grignard reagent and consequently that the chirality of the carbinols must result from a specifically orientated complex - carbonyl compound interaction.

In other types of asymmetric synthesis such as RMgX—R'COR" reactions where R' or R" is asymmetric and where the stereoselectivity may be anticipated by application of Cram (7) or Prelog (8) type rules, it has been possible in many instances to rationalise the results in terms of "bulk" effects or in terms of coordinated transition states which control the preferred direction of addition. The results presented in Table 1 do not lend themselves to such treatment. For the purposes of discussion it can be assumed that in the R'COR" - (RMgX -sugar) transition state the R' and R" groups will be associated respectively with specific areas of the sugar-Grignard complex A and B, and that the incoming group attacks the carbonyl carbon from below the plane of the paper. Then to account for the observed configuration of the products in Table 1, R' and R" must be associated with areas A and B as shown in Table 2.



From these results it is clear that "bulk" effects do not provide a simple explanation why the phenyl group in reaction 4 occupies a different position to the phenyl group in reaction 7 or why the methyl groups in reactions 2 and 3 do not occupy equivalent positions. It is of course possible that with complex chiral compounds such as (I) a number of equally probable transition states are possible but with the evidence at present available further speculation is not justified.

A number of other sugar derivatives also proved effective in promoting the asymmetric synthesis of carbinols. Among these were 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose, 1,2:3,4-di-O-isopropylidene-L-rhamnitol and 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose.

TABLE 2

Orientation of Carbonyl-(Sugar-Grignard Complex) to account for Observed Chirality

| Reaction | Site A<br>R′ | Site B<br>R″ | R | Configuration |
|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_{11}$ | $CH_3$ | R |
| 2 | $CH_3$ | $C_6H_{11}$ | $C_6H_5$ | S |
| 3 | $C_6H_5$ | $CH_3$ | $C_6H_{11}$ | S |
| 4 | $C_6H_5$ | $CH_3$ | $C_2H_5$ | S |
| 5 | $CH_3$ | $C_2H_5$ | $C_6H_5$ | S |
| 6 | $C_6H_5$ | $C_2H_5$ | $CH_3$ | R |
| 7 | H | $C_6H_5$ | $C_2H_5$ | R |
| 8 | $C_2H_5$ | H | $C_6H_5$ | R |

Of the fully blocked sugar derivatives investigated methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside (II) was most effective and in its presence in benzene the MeMgI - $C_6H_5COC_6H_{11}$ reaction afforded R(+)cyclohexylmethylphenylcarbinol in 50 % optical yield. Perhaps significantly in ether in the presence of methyl-4,6-benzylidene-α-D-glucopyranoside, S(-)cyclohexylmethylphenylcarbinol was the preferred product from the MeMgI-$C_6H_5COC_6H_{11}$ reaction.

Recent papers (9,10) have demonstrated the utility of sugar derivatives as satisfactory substrates for highly stereoselective Cram and Prelog type reactions where the carbonyl group is covalently linked to the sugar. This paper demonstrates that substituted sugars may also provide a suitable environment for studies of a third type of asymmetric synthesis where the sugar and carbonyl compound are not covalently linked.

## REFERENCES

1. C. Blomberg and J. Coops, Rec.Trav.Chim., 83, 1083 (1964).
2. H.L. Cohen and G.F. Wright, J.Org.Chem., 18, 432 (1953).
3. N. Allentof and G.F. Wright, J.Org.Chem., 22, 1 (1957).
4. W. French and G.F. Wright, Can.J.Chem., 42, 2474 (1964).
5. T.D. Inch, R.V. Ley and P. Rich, J.Chem.Soc.(C), 1693 (1968).
6. P. Vink, C. Blomberg, A.D. Vreugdenhill and F. Bickelhaupt, Tetrahedron Letters, 6419 (1966).
7. D.J. Cram and F.A. Abd Elhafez, J.Am.Chem.Soc., 74, 5828 (1952).
   D.J. Cram and K.R. Kopecky, J.Am.Chem.Soc., 81, 2748 (1959).
8. V. Prelog, Helv.Chim.Acta, 36, 308 (1953).
9. T.D. Inch et al., Carbohydrate Res., 5, 45 (1967). J.Chem.Soc.(C), 1683, 1968.
10. M. Kawana and S. Emoto, Bull.Chem.Soc. Japan, 40, 2168 (1967).