Stereospecificity and Catalysis *via* Chelation in Grignard Reactions of Some β-Hydroxy-ketones

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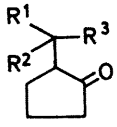
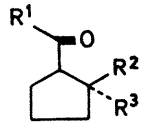
Summary Chelation in the transition state affects Grignard reactions with 2-α-hydroxyalkyl- (or α-hydroxyaryl)-cyclopentanones and 2-benzoyl-(or acyl)-cyclopentanols.

THE influence of intramolecular chelation on the chemical behaviour of β-hydroxy-ketones which are part of enolic or aromatic systems (*e.g.* enolized β-diketones or 2-hydroxyphenyl ketones) is well documented. The stereoselectivity observed in Grignard reactions of acyclic α-hydroxy-ketones, as predicted by chelated models,[1] has not been attained in analogous reactions with open-chain saturated β-hydroxy-ketones.[2]

We now report results on the relationship between chelation and reactivity in Grignard reactions of β-hydroxy-ketones in which one oxygen function is situated on a cyclopentane ring.

Grignard reactions of β-hydroxycyclopentanones and β-oxocyclopentanols[a]

Compound[b]		Reagent	Yield of isomers[c]		Overall yield[c]
					
(I)	$R^1=R^2=Ph$; $R^3=OH$	MeMgBr	100[e]		68
(II)[d]	$R^1=H$; $R^2=Ph$; $R^3=OH$ ..	MeMgI	100[e]		71
(III)	$R^1=R^2=Me$; $R^3=OH$ ..	PhMgBr	100[e]		60
(IV)	$R^1=R^2=H$; $R^3=OH$	PhMgBr	100[e]		32
(V)	$R^1=R^2=Ph$, $R^3=H$	MeMgI	55[e]	45[f]	72
					
(VI)	$R^1=Me$; $R^2=OH$; $R^3=H$ ..	PhMgBr	100[e]		73
(VII)	$R^1=Ph$; $R^2=OH$; $R^3=H$ ..	MeMgBr	6[e]	94[e]	82
		PhMgBr	100[e]		72
(VIII)	$R^1=Ph$; $R^2=H$; $R^3=OH$ ..	MeMgBr	36[f]	64[f]	24
		PhMgBr		100[f]	8

[a] An ether solution of ketone was added to an ice-cooled 6-fold excess of Grignard reagent in solution in dry ether; the reaction was continued at room temperature for 4 h followed by hydrolysis with cold saturated solution of NH_4Cl. Compound (VII) was treated with MeMgBr without cooling. [b] New compounds gave satisfactory analytical and spectroscopic data. [c] Yields were determined by chromatography and n.m.r. analysis. [d] Isometrically pure. [e] *cis*-Diol. [f] *trans*-Diol.

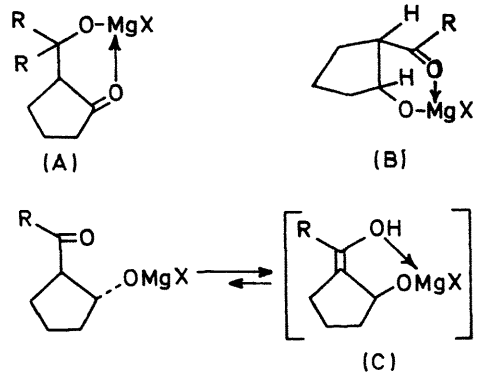
Reactions of β-hydroxycyclopentanones (I)—(IV) (see Table) with Grignard reagents in ether solution proceeded with complete stereospecificity. The *cis*-configuration of the diols formed by addition *via* chelated models (A) was

confirmed by the presence of i.r. absorption attributable to intramolecularly bonded OH [$\Delta\nu$(OH) 125—130 cm^{-1}).† Preferential steric approach[3] in similar nonchelated systems was not a sufficient condition for high stereoselectivity, as shown by Grignard addition to compound (V).

Stereospecificity was also observed in additions to *cis*-β-oxo-cyclopentanols. The pure diol formed from *cis*-2-acetylcyclopentanol (VI) and phenylmagnesium bromide was diastereoisomeric with the major diol obtained from *cis*-2-benzoylcyclopentanol (VII) and methylmagnesium bromide. The steric factor in these additions would be less significant than in the previous cases if not correlated with the chelation, which implies a *cis*-fused bicyclic model (B) and thus preferential attack from the *exo*-side.

Absence of chelation‡ in the reaction of *trans*-2-benzoylcyclopentanol (VIII) with methylmagnesium bromide resulted in low stereoselectivity and low addition yield. Similarly, reaction of (VIII) with a large excess of phenylmagnesium bromide gave only 8% of *trans*-diol along with 13% of (VII), 28% of (VIII), and 24% of 2-benzoylcyclopentene. Use of (VIII) deuteriated at the α-position afforded the same mixture of ketones, devoid of deuterium.§ Accordingly, the equilibrium was displaced towards enolized (VIII) enabling chelation by flattening of the molecule [model (C)] to occur. Reaction of the *cis*-isomer (VII) with phenylmagnesium bromide gave 72% of *cis*-diol.

The relationship between configuration, chelation, and behaviour in Grignard reactions seems to be specific for the



systems described containing a cyclopentane ring. Preliminary results obtained with cyclohexane homologues suggest that the formation of chelated rings analogous to (A) and (B) is more difficult, as reflected in low yields of *cis*-diols.

(*Received, February 11th*, 1971; *Com.* 131.)

† *trans*-Diols were almost devoid of intramolecular hydrogen bonding.

‡ This assumption is made on the basis of steric strain and absence of hydrogen bonding in the hydroxy-stretching frequency of the reactant.

§ As found by mass spectral analysis.

[1] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, 1959, **81**, 2748.

[2] T. J. Leitereg and D. J. Cram, *J. Amer. Chem. Soc.*, 1968, **90**, 4019.

[3] H. E. Zimmerman and J. English, *J. Amer. Chem. Soc.*, 1954, **76**, 2285, ascribed the isolation of a single diol in some Grignard reactions with β-hydroxycyclohexanones to steric approach control.