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ASYMMETRIC SYNTHESIS. PART V. ACETYLENIC CARBINOLS

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In a previous paper it was shown that, in ether solution, addition reactions to dissymmetric ketones, of Grignard reagents that were complexed with 1,2:5,6-di-O-isopropylidene-*D*-glucofuranose (I) were highly stereoselective affording asymmetric carbinols in high optical yield.[1] We now report that an attempt to prepare optically active 1-cyclohexyl-1-phenylprop-3-yn-1-ol (II) by reaction of cyclohexylphenylketone with an ethynyl magnesium bromide —(I) complex in ether, using reaction conditions[1] that for non-acetylenic Grignard reagents afforded maximum yields and maximum optical yields of carbinols, was unsuccessful presumably because of the poor solubility of acetylenic Grignard reagents in ether. However, when ether was replaced as solvent by tetrahydrofuran treatment of cyclohexylphenylketone with the (I) — $HC\equiv CMgBr$ complex afforded II (75%) with $[\alpha]_D^{20}$ + 0.67° (*c*, 40 in chloroform). The optically active II, was converted into 2-cyclohexyl-2-hydroxy-2-phenylacetaldehyde, $[\alpha]_D$ - 6.94° (*c*, 2 in chloroform) by successive partial reduction, osmium tetraoxide hydroxylation and sodium periodate oxidation. Since (-)-2-cyclohexyl-2-hydroxy-2-phenylacetaldehyde has the R-configuration[2] and when optically pure has a specific rotation of -230° it follows that the optical yield of S(+)1-cyclohexyl-1-phenylprop-3-yn-1-ol was only 3%. It is of interest that although the optical yield in tetrahydrofuran was low the steric course of the reaction of the ethynyl Grignard reagent - sugar complex with cyclohexylphenylketone was the same as the MeMgI — cyclohexylphenylketone reaction in ether which afforded preponderantly (*R*)cyclohexylmethylphenylcarbinol[1].

In an attempt to improve the optical yield of II the reactions in ether of $RCOC\equiv CH$ (in this paper R = cyclohexyl) with a PhMgBr — I complex and of $PhCOC\equiv CH$ with a RMgBr — (I) complex were examined. [The practical procedure used in each case was to add the ethynyl ketone (1 mol) to the complex from Grignard reagent (3.5 mol) and I (2 mol) at room temperature and to monitor the reaction by t.l.c. with mixtures of ether - light petroleum (b.p. 60 - 80°), ether - benzene or acetone - light petroleum (b.p. 60 - 80°) as solvents. Column chromatography over silica (Merck) in one or more of the above solvent mixtures was used to purify the products which had elemental analyses, and i.r. and n.m.r. spectroscopic data consistent with the assigned structures]. In the former case two products were obtained each in 40% yield presumably by the sequence of reactions shown in Scheme 1. The first product, an optically inactive (*c*, 40 in $CHCl_3$) syrup, was II and the second was IV m.p. 87° (from ethanol), $[\alpha]_D^{20}$ + 2 (*c*, 2 in $CHCl_3$). In the latter case three products were obtained:- a) II (37%) $[\alpha]_D^{20}$ - 0.85° (*c*, 2 in $CHCl_3$); b) VII (12%) m.p. 120° (from light petroleum, b.p. 40 - 60°), $[\alpha]_D$ *ca.* 0° (*c*, 2 in $CHCl_3$); c) VI (12%), m.p. 88 - 90° (from light petroleum, b.p. 40 - 60°), $[\alpha]_D^{20}$ - 1.07° (*c*, 4 in $CHCl_3$). The sequence of reactions leading to VI and VII is presumably as illustrated in Scheme 2. The intermediate III (Scheme 1) and V (Scheme 2) were not isolated but evidence for their formation was provided when V was isolated in high yield from the direct reaction of PhCOC ≡ CH with 0.5 molar equivalent of MeMgI in ether.

The finding that II, formed in the RCOC ≡ CH — (PhMgBr - I) reaction was optically inactive was unexpected particularly since IV had appreciable optical activity. This result suggests that RCOC ≡ CMgBr coordinates with I in preference to the formation of a PhMgBr - I coordinated complex. No such distinction was apparent in the PhCOC ≡ CH — (RMgBr - I) reaction in which the products II and VII were both optically active. However the optical yield (4%) of II produced by the PhCOC ≡ CH — (RMgBr - I) reaction in ether was only marginally better than that observed in II formed in the RCOPh — (CH ≡ CMgBr - I) reaction in tetrahydrofuran and was much lower than would have been predicted since the corresponding PhCOMe — RMgBr reaction afforded S(-)Ph(R)(Me)·C·CH in 28% optical yield. The variable optical yields of the products from reactions of Grignard reagents complexed with (I) and ethynyl ketones serve to demonstrate further the complexity of the coordinating effects between sugars and Grignard reagents.

Although there have been many reports[3] of reactions between α,β-unsaturated (olefinic) ketones and Grignard reagents the reactions of acetylenic ketones and Grignard reagents have been little investigated and consequently a number of points arising from the reactions illustrated in Schemes 1 and 2 are worthy of comment. Both the RMgBr — PhCOC ≡ CH and PhMgBr — RCOC ≡ CH reactions show that whereas 1,2-addition reactions to ethynyl ketones occur preferentially when the acetylene group is terminal, 1,4-addition reactions preponderate when the triple bond forms part of a carbon chain. The rapidity of the 1,4-addition reactions to the non-terminal acetylenic bonds contrasted sharply with the apparent reluctance of IV and VI to undergo 1,4-addition reactions across the olefinic bond although facile 1,4-addition to VI resulted in aromatic substitution and the formation of VII. It is also of interest that whereas both $PhCOC \equiv CH$ and $RCOC \equiv CH$ readily formed Grignard reagents which participated in further reactions no products were detected to indicate further reactions of Grignard reagents formed from IV, VI or VII when the reactions were carried out under the controlled conditions described. Even when $PhCOC \equiv CH$ was treated with an excess of RMgBr for prolonged reaction times II and VII were still the preponderant products although a multiplicity of other compounds were detected by t.l.c.

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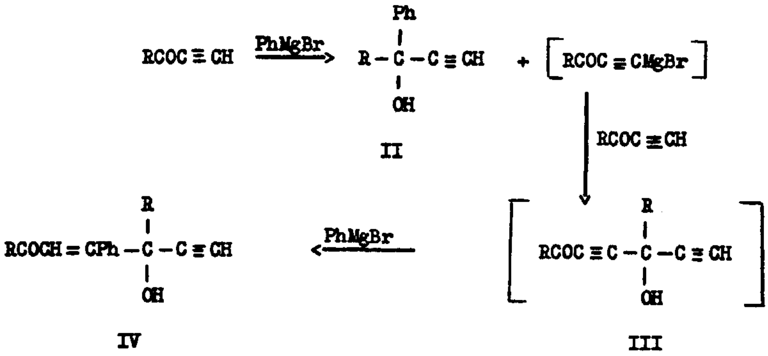
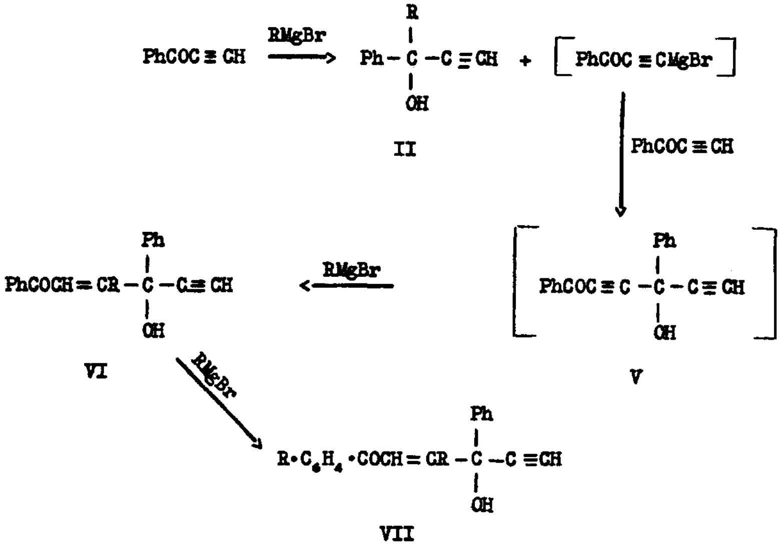


Scheme 1



Scheme 2