# SEVEN-CARBON ANNELATION. SYNTHESIS OF SUBSTITUTED SPIROCHROMANS (3,4-DIHYDRO-SPIRO[2H-1-BENZOPYRAN-2,1'-CYCLOHEPTANES])

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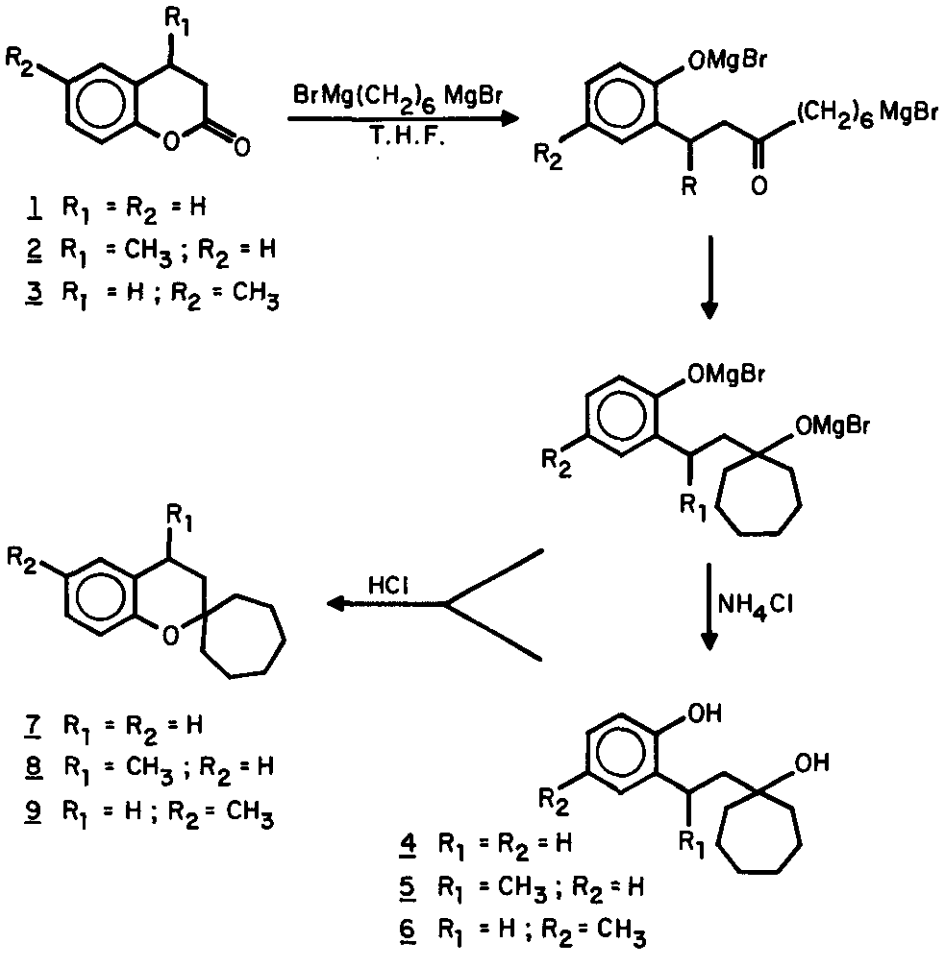
Abstract - The use of 1,6-di(bromomagnesio)hexane in tetrahydrofuran leads after double addition at the carbonyl of substituted chromans to the formation of seven membered dihydroxycompounds. Subsequently the title compounds are formed by simple treatment with dilute acid and distillation.

Examination of past and present literature shows the lack of a general method of preparation of substituted spirochromans. We have been interested in annelative techniques for cyclopentane and cyclohexane construction[1-3] particularly those widely used in the synthesis of spiro ring systems and specially for spirohetero aromatic compounds[5]. We wish to report a new synthesis involving seven-membered spiroannelation which is illustrated by the synthesis of 3,4-dihydrospiro [2H-1-benzopyran-2,1'-cycloheptane] as shown in scheme 1. It has been reported[4] that the 1,6-di(bromagnesio)hexane does not react with butyrolactone to afford ω-hydroxyalkylcycloheptanol, but rather leads to a mixture of different products from which the isolation of the annelative compound was not possible.

In this present work however we have found that the annelation product is the major compound in the reaction of the 1,6-di(bromomagnesio)hexane with substituted chromanones in an appropriate solvent such as tetrahydrofuran. We have observed that the ratio of annelation vs open chain products to be highly dependent of the substrate structure[5] and also on the size of the new formed ring. The by-products obtained arise mostly from the initially formed ketone by intermolecular attack of a second bifunctional Grignard reagent and there is some recovery of starting material. The temperature of addition is not critical but since the reaction is exothermic, is usually affected in the cold. A solution of the dihydrocoumarin in an inert and anhydrous solvent such as benzene or tetrahydrofuran is added at a rate sufficient to control the exothermic reaction. After the end of the addition, the resultant suspension was stirred and kept at room temperature overnight. This suspension persists under reflux and a clear solution is not obtained with the 1,6-di(bromomagnesio)alkane under the conditions employed in our procedure with the two other Grignard reagent previously reported. The crude mixtures were routinely hydrolyzed with




aqueous acid and the presence of the diol confirmed by IR and NMR analysis[6]. The intermediate diols can be isolated by conventional methods (column chromatography, fractional distillation) or the crude diols can be used without purification for direct conversion to the cyclic ethers by the action of an appropriate acid. This present method for the preparation of such spiro compounds by seven carbon annelation is reported here for the first time and only for this class of compound, and represents another example of the utility of diGrignard reagents in organic synthesis. This one-step reaction without isolation of the intermediate is most convenient.

Di(bromomagnesio)alkanes; General Procedure:

The 1,6-dibromohexane (16.8 g, 0.069 mol) dissolved in anhydrous tetrahydrofuran (150 mL) is added to magnesium turnings (3.5 g, 0.15 g - atom), under a stream of nitrogen. A small volume of the dihalide solution is added to cover the magnesium and the stirring is started. The exothermic reaction starts within a few min. The rest of the dihalide solution is added dropwise, at a rate *slow enough to avoid excessive heating (40-50°). After the addition is completed, the clear* solution is allowed to stir 4 h at room temperature. The yield of the Grignard reagent is

determined by the Gilman procedure[7].

To this organomagnesium compound prepared (0.06 mol) is added dropwise at room temperature the dihydrocoumarin 1 (5.92 g, 0.04 mol) in anhydrous tetrahydrofuran (50 mL). The reaction mixture is stirred overnight under an atmosphere of nitrogen. After hydrolysis with saturated aqueous ammonium chloride, the mixture is extracted with ether, washed with water and dried with sodium sulfate. The solvents are removed under reduced pressure and the crude product obtained is used directly for the etherification reaction. A mixture of this crude sample and 36% hydrochloric acid (15 mL) is heated under reflux for 6 h. After cooling, the resulting mixture is diluted with water, extracted with ether, the extracts washed with water and dried with sodium sulfate. The solvent is removed in vacuo and the product distilled.

3,4-Dihydrospiro[2H-1-benzopyran-2,1'-cycloheptane] (7)

bp 112-114°C (0.01 mm Hg); 20% yield (from dihydrocoumarin); IR $\nu_{max}$ (neat) 1240, 1040 $cm^{-1}$; NMR $\delta$ 1.12-2.21 (m, 14 H), 2.52-2.91 (t, 2H, J = 7 Hz), 6.64-7.18 (m, 4H); mass spectrum (relative intensity) m/e 216 ($M^+$, 54%), 107 ($M^+-C_8H_{13}$, 100%).

3,4-Dihydro-4-methyl-spiro[2H-1-benzopyran-2,1'-cycloheptane] (8)

bp 99-101°C (0.02 mm Hg); 14% yield (from 4-methyl-dihydrocoumarin); IR $\nu_{max}$ (neat) 1240, 1045 $cm^{-1}$; NMR $\delta$ 1.3 (t, 3H, J = 7 Hz), 1.2-2.2 (m, 14H), 6.7-7.2 (m, 4H); mass spectrum (relative intensity) m/e 230 ($M^+$, 58%, 121 ($M^+-C_8H_{13}$, 100%).

3,4-Dihydro-6-methyl-spiro[2H-1-benzopyran-2,1'-cycloheptane] (9)

bp 114-116°C (0.01 mm Hg); 15% yield (from 6-methyl-dihydrocoumarin); IR $\nu_{max}$ (neat) 1238, 1040 $cm^{-1}$; NMR $\delta$ 0.9-2.2 (m, 15H), 2.25 (s, 3H), 2.5-2.9 (t, 2H, J = 7 Hz), 6.5-7.1 (m, 3H); mass spectrum (relative intensity) m/e 230 ($M^+$, 61%), 121 ($M^+-C_8H_{13}$, 100%).

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