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A NOVEL GRIGNARD ADDITION TO A COUMARIN

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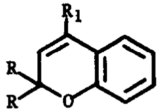
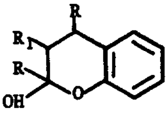
The well documented reaction of Grignard reagents with coumarins(1) is known to give different products which depend on the position of the substituents. Coumarins substituted in the 4-position give 2,2,4-trisubstituted Δ^3-chromenes I whereas 3-substituted coumarins give 2,3,4-trisubstituted chromanols II. These products result by the addition of two moles of Grignard reagent, the former by 1,2 addition and the latter by 1,2 and 1,4 addition. However, with limited amounts of phenyl Grignard reagents, monoaddition may occur to yield 2-substituted chromenols III. In all cases the first mole of the reagent adds to the carbonyl group.



I



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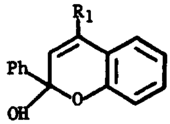
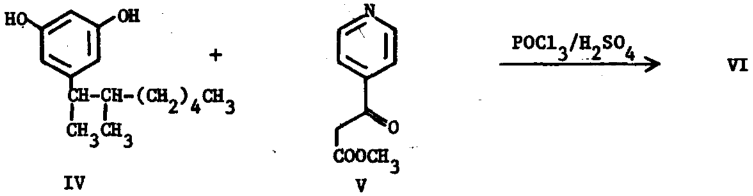


III

We wish to report in this communication a novel Grignard reaction with a 4-pyridylcoumarin where three moles of Grignard reagent are added. The first two moles add by 1,2 addition followed by the addition of the third mole to the double bond of the Δ^3-chromene to yield 2,2,3,4-tetrasubstituted chroman IX.

5-(3-Methyl-2-octyl)resorcinol (IV)(2) was allowed to react with methyl 3-oxo-3-(4-pyridyl)propionate (V)(3) in the presence of concentrated sulfuric acid and phosphorous oxychloride(4) at room temperature for 48 hr. Neutralization and extraction with ether gave the intermediate coumarin(5) (VI), mp 191-193° (aqueous ethanol, 80% yield), λ_{max}^{EtOH} 315 mμ (ε 11,700). The nmr spectrum(6) of VI agreed with the assigned structure.



IV

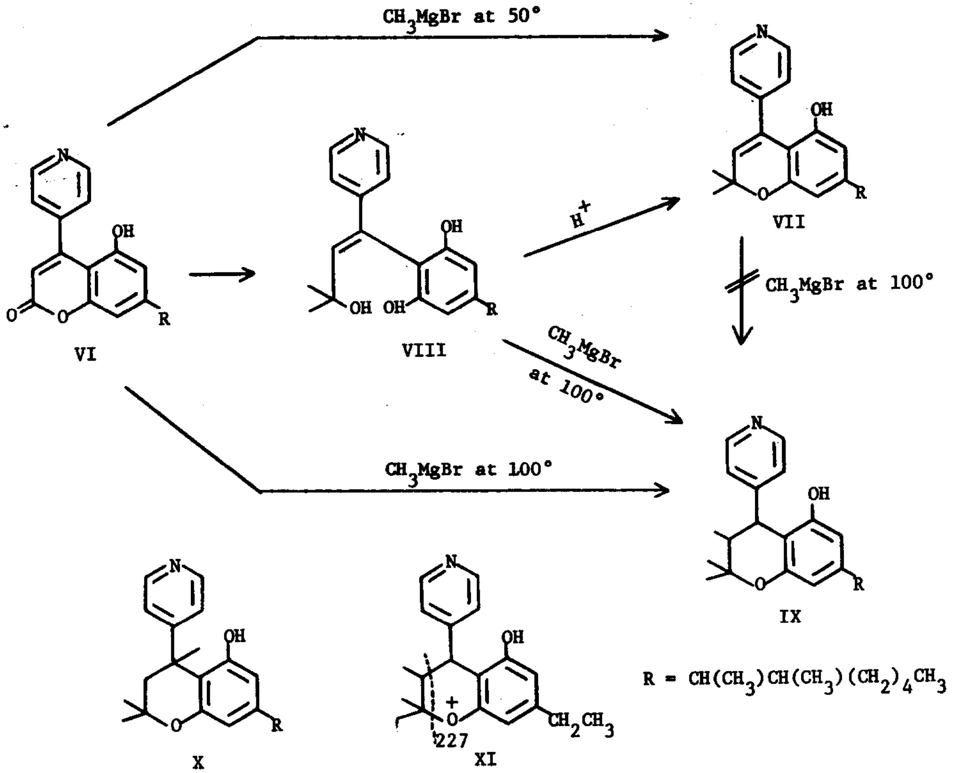
V

We have found that treating a suspension of VI in anisole with excess methylmagnesium bromide in anisole (prepared in ether and then replaced with anisole) at 50° for 16 hr, followed by decomposition of the reaction mixture with sulfuric acid and removal of anisole by steam distillation, yielded VII, mp 80-85° (acetonitrile, 60% yield), λ_{max}^{EtOH} 290 mμ (ε 6,350), 263 mμ (ε 10,160). The nmr of VII was consistent with the assigned structure.

However, if the Grignard reaction was carried out at 100° for 48 hr and worked up in a similar manner, a gum was obtained which crystallized from acetonitrile to give IX, mp 193-195°,$^{(7)}$ λ_{max}^{EtOH} 283 mμ (ε 1,680), 262 mμ (ε 2,520). Its mass spectrum shows (inter alia) peaks at m/3 395, 325 ($M^+-C_5H_{10}$), 297 ($M^+-C_7H_{14}$), 227 ($297-C_5H_{10}$). The mass spectrum allows one to distinguish between IX and X principally on the basis of the fragmentation from 297 to 227 corresponding to the cleavage as shown in XI. This choice is further supported by the nmr spectrum which exhibits a one proton doublet at 3.51 ppm (J = 10 cps) assignable to H-4 (in IX). The coupling constant suggests that the methyl group at 3-position is trans to the pyridyl group.

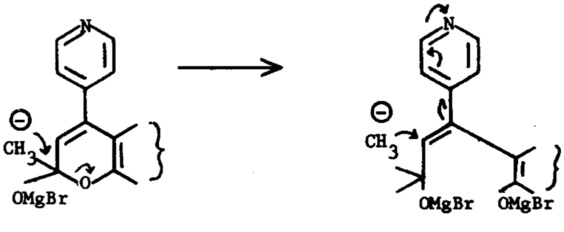
In order to learn the mode of formation of IX, we reacted the pyrone VI with excess methylmagnesium bromide as before at 50° for 16 hr and then decomposed the complex with ammonium chloride. Anisole was removed in vacuo and the residue was purified by chromatography on silicic acid (ethyl acetate). The triol VIII was obtained as a gum (50% yield), λ_{max}^{EtOH} 247 mμ (ε 12,900). In agreement with the assigned structure, the nmr spectra of VIII had absorption at 1.30(s) (area 6, gem dimethyl group), 6.34(s) (2, benzene ring), 6.63(s) (1, vinyl) and 6 to 7 ppm (br) (3, exchangeable with D_2O).

When part of the triol VIII was treated with a few drops of 48% hydrobromic acid in refluxing heptane, a product identical with VII in all respects was obtained (60% yield). Treatment of VIII with excess methylmagnesium bromide at 100° for 48 hr (the conditions used for the preparation of IX) furnished a crystalline product (20% yield) identical with IX in all respects. IX was also obtained when the pyrone VI was treated with excess methyllithium in ether. However, VII could not be converted to IX by treatment with excess methylmagnesium bromide at 100°.



R = $CH(CH_3)CH(CH_3)(CH_2)_4CH_3$

It is therefore clear that the action of Grignard reagent on VI proceeds by addition to the carbonyl group (XII) followed by attack by another mole with ring opening to give the intermediate XIII.(1,8,9) This is in contrast to the evidence of Shriner and Sharp on the reaction of methyl Grignard reagent on coumarin.(10) At higher temperature, because of the electron-withdrawing properties of the complex of pyridine with the excess reagent and the fact that the pyridine ring can become coplaner with the double bond in XIII, an additional mole of reagent



adds to the double bond. The restricting influence on coplanarity in the closed ring compound VII prevents this addition and hence the lack of conversion of VII to IX. This becomes clear from an examination of the dreiding model of VII which shows that the pyridine ring is out of plane with the double bond. In this connection it is interesting to compare the vinyl proton signals in the nmr spectra of VII and VIII which appear as singlets at 5.57 and 6.63 ppm respectively.

The addition of the third mole of Grignard to VIII is another example of the electrophilic reaction of a 4-vinylpyridine.(11) However, as far as we are aware, Grignard addition to 4-vinylpyridine system has not been reported. 2- and 4-Vinylpyridines are known to polymerize in the presence of alkyl magnesium halides.(12)

The scope of this reaction is being further investigated.

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5. Satisfactory analytical data have been obtained for all new compounds.
6. All nmr spectra were determined on a Varian A-60 spectrometer in $CDCl_3$. Values are given in parts per million relative to TMS as an internal standard: s, singlet; d, doublet; t, triplet; br, broad.
7. The total yield was 20%, but it included fractions varying in melting points from 166 to 195°. Elemental and spectral data confirmed these fractions to be mixtures of threo and erythro diastereoisomers.
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