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Reactions between Grignard Reagents and Ethyl 4-Methyl-3-coumarincarboxylate

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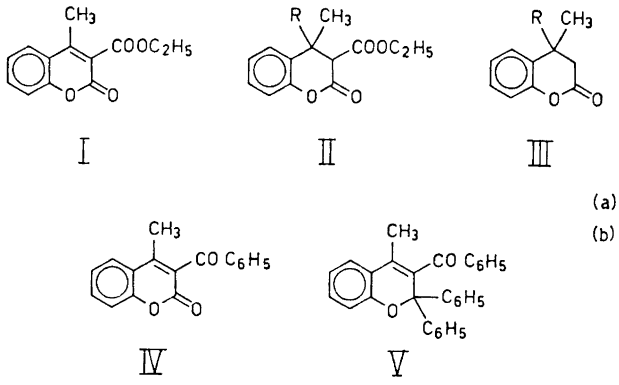
Ethyl 4-methyl-3-coumarincarboxylate reacts with methylmagnesium iodide and isopropylmagnesium bromide forming 1,4-addition products. In contrast to these Grignard reagents, phenylmagnesium bromide gives 1,2-addition reactions. The carbonyl group in the carbethoxy portion is first attacked, and this reaction is then followed by a double 1,2-addition to the carbonyl group of the lactone ring.

The reactions of ethyl 3-coumarincarboxylate with phenylmagnesium bromide and *o*-methoxyphenylmagnesium iodide have been examined earlier in this laboratory.[1,2] A 1,4-addition of the Grignard reagent to the conjugated double bond system C=C–C=O occurred in both cases. This reaction was, however, followed by different 1,2-additions to the carbonyl groups.

When Munch-Petersen [3] recapitulated the results of earlier investigations into the reactions of Grignard reagents with α,β-unsaturated carboxylic esters, he noted among other things that the presence of two substituents at the β carbon atom of the ester prevents, or strongly represses, the 1,4-addition reactions and so often favours 1,2-addition reactions.

Against this background, it seemed justifiable to examine the reactions between Grignard reagents and ethyl 4-methyl-3-coumarincarboxylate (I), in which the methyl group may be taken as the second substituent at the β carbon atom. Methylmagnesium iodide, isopropylmagnesium bromide, and phenylmagnesium bromide were chosen as suitable Grignard reagents.

Methylmagnesium iodide gave exclusively a 1,4-addition reaction with the coumarin derivative. The product, ethyl 4,4-dimethyl-3,4-dihydro-3-coumarincarboxylate (II a), was transformed into 4,4-dimethyl-3,4-dihydrocoumarin (III a) by alkaline hydrolysis. Isopropylmagnesium bromide reacted in the same way, but gave a mixture of 4-isopropyl-4-methyl-3,4-dihydrocoumarin (III b) and its 3-carbethoxy derivative (II b). Apparently, the ester was the primary product. It was obviously partly hydrolysed when the products were isolated.



Phenylmagnesium bromide reacted in quite a different way. A large excess of the Grignard reagent gave, besides biphenyl, 3-benzoyl-2,2-diphenyl-4-methyl-2*H*-1-benzopyran (V). If a smaller excess was used, 3-benzoyl-4-methylcoumarin (IV) was also formed. It follows that the first reaction to occur was a 1,2-addition of the Grignard reagent to the carbonyl group of the ester portion. This reaction was then followed by a double 1,2-addition to the carbonyl group of the lactone ring. The dihydroxy derivative formed as primary product in the latter reaction apparently splits off water to form the benzopyran derivative during the work up. Similar reactions have been reported by Heilbron and Hill.[4]

It is interesting to note that the course of the reactions was dependent on the aliphatic or aromatic nature of the Grignard reagent.

The NMR spectra of 4,4-dimethyl- and 4-isopropyl-4-methyl-3,4-dihydrocoumarin are of note. The spectrum of the former compound is composed of a singlet from the methylene protons in position 3, a singlet from the methyl protons, and a complex signal from the phenylene protons. The spectrum of the latter shows a distinct AB quartet signal from the methylene protons in position 3 and signals with the appropriate multiplicity from the protons of the methyl, isopropyl, and phenylene groups. Thus, the 4,4-dimethyl-3,4-dihydrocoumarin molecule is not rigid, but the conformations can easily pass over one into the other. On the other hand, the isopropyl group in the molecule of 4-isopropyl-4-methyl-3,4-dihydrocoumarin prevents, or at least represses, conformation changes.

EXPERIMENTAL

Ethyl 4-methyl-3-coumarincarboxylate (I) was prepared from ethyl cyanoacetate and *o*-hydroxyacetophenone according to Wiener *et al.*[5] An attempt to hydrolyse the first intermediate, 3-cyano-4-methylcoumarin in alkaline solution in the presence of pyridine at ordinary temperature according to Schroeder and Link [6] was not successful.

Action of methylmagnesium iodide. A solution of ethyl 4-methyl-3-coumarincarboxylate (2.00 g) in dry ether (150 ml) was gradually added to a Grignard reagent prepared from methyl iodide (3.77 g), magnesium (0.63 g), and dry ether (20 ml). The reaction mixture was warmed for 15 min and then poured into a mixture of ice, water, and hydrochloric acid. The ether phase was separated and dried with sodium sulphate. The oil that remained

when the solvent had been evaporated was analysed by gas chromatography (column 1/8″ × 1.5 m, stationary phase 5 % SE-30 on Chromosorb W, flow rate of nitrogen 22 ml/min, initial temperature 150°, temperature programming 10°/min). Only one component was detected. The mass spectrum taken on a combined gas chromatograph/mass spectrometer showed the following important ions: $M^{+\cdot}$ at *m/e* 248, calc. 248; $(M-CH_3)^+$ at *m/e* 233; $(M-OC_2H_5)^+$ at *m/e* 203; $(M-CH_4-OC_2H_5)^+$ at *m/e* 187. These data indicated that the compound was ethyl 4,4-dimethyl-3,4-dihydro-3-coumarincarboxylate.

A sample (1.58 g) of the oil obtained above was dissolved in ethanol (40 ml), and a solution of potassium hydroxide (0.4 g) in water (0.5 ml) and ethanol (16 ml) was added. The mixture was boiled for 4 h under reflux. Because no crystals separated despite the chilled mixture being stored overnight in the refrigerator, the solvent was evaporated and the residue dissolved in a mixture of ether and water. The ether phase was dried with sodium sulphate and the solvent was evaporated. Gas chromatographic analysis of the remaining oil (0.49 g) showed only one compound, the mass spectrum of which was identical with that of 4,4-dimethyl-3,4-dihydrocoumarin. The sample of this compound prepared according to Colonge and Chambard [7] gave the following NMR spectrum: 4 aromatic protons at τ 2.4 – 3.2, 2 methylene protons (singlet) at τ 7.49, and 6 methyl protons (singlet) at τ 8.68.

The alkaline water solution was acidified and extracted several times with ether. The ether solutions were combined and dried with sodium sulphate. After the solvent had been evaporated, an oil (0.56 g) remained. The main part consisted of 4,4-dimethyl-3,4-dihydrocoumarin.

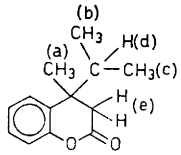
Action of isopropylmagnesium bromide. A solution of ethyl 4-methyl-3-coumarincarboxylate (5.00 g) in dry ether (400 ml) was gradually added to a Grignard reagent prepared from isopropyl bromide (5,31 g), magnesium (1.04 g), and dry ether (40 ml). After 12 h, the mixture was poured into a mixture of ice, water, and hydrochloric acid. The ether phase was separated and dried with sodium sulphate. When the ether had been evaporated, an oil (4.62 g) remained. The gas chromatographic analysis revealed that it consisted of 4-isopropyl-4-methyl-3,4-dihydrocoumarin (56.4 mol %), ethyl 4-isopropyl-4-methyl-3,4-dihydro-3-coumarincarboxylate (30.5 mol %), and unreacted ethyl 4-methyl-3-coumarincarboxylate (13.1 mol %). The compounds were identified by the aid of mass spectra.

4-Isopropyl-4-methyl-3,4-dihydrocoumarin: $M^{+\cdot}$ at *m/e* 204, calc. 204; $(M-C_3H_7)^+$ at *m/e* 161.

Ethyl 4-isopropyl-4-methyl-3,4-dihydro-3-coumarincarboxylate: $M^{+\cdot}$ at *m/e* 276, calc. 276, $(M-C_3H_7)^+$ at *m/e* 233; $(M-OC_2H_5)^+$ at *m/e* 231; $(M-C_3H_7-H)^+$ at *m/e* 232, $(M-COOC_2H_5)^+$ at *m/e* 203; $(M-C_3H_8-OC_2H_5)^+$ at *m/e* 187.

Because the products could not be separated, they were hydrolysed in the way described above for the alkaline hydrolysis of ethyl 4,4-dimethyl-3,4-dihydro-3-coumarincarboxylate. Only one substance, 4-isopropyl-4-methyl-3,4-dihydrocoumarin, could be detected in the resulting ether solution. The substance was very pure. After a careful evaporation of the solvent, the remaining oil gave an excellent NMR spectrum (Table 1). The IR spectrum of the substance shows a strong carbonyl absorption at 1785 cm^{-1}.

Table 1. Chemical shifts (τ), coupling constants (*J*), intensties, and multiplicities of the signals in the NMR spectrum of 4-isopropyl-4-methyl-3,4-dihydrocoumarin.

	Proton(s)	τ	Intensity	Multiplicity	*J*
	Aromatic	2.6 – 3.3	4		
	a	8.83	3	Singlet	
	b, c	9.20	3	Doublet	
		9.26	3	Doublet	6.7
	d	8.26	1	Septet	
	e	7.22	2	AB system	15.7
		7.92			

The alkaline water solution contained mainly 4-methyl-3-coumarincarboxylic acid.

Action of phenylmagnesium bromide. Experiment 1. Ethyl 4-methyl-3-coumarincarboxylate (5.80 g) dissolved in dry benzene (60 ml) was gradually added to a Grignard reagent prepared from bromobenzene (13.74 g, 3.5 equiv.), magnesium (2.10 g), and dry ether (40 ml). The addition was completed in 20 min and the mixture was warmed in a water-bath for 15 min. The reaction mixture was poured into a mixture of ice, water, and hydrochloric acid. The ether phase was separated, washed with water and potassium hydrogen carbonate, and finally dried with sodium sulphate. The gas chromatographic analysis of the oil obtained after evaporation of the solvent showed that biphenyl, unreacted ethyl 4-methyl-3-coumarincarboxylate, and a new compound (main product) were present. A smeary sample of the last-mentioned compound was obtained when the oil was dissolved in ethanol and ligroin was added to the cold solution. After the mixture had been kept for some days in the refrigerator, the precipitate was filtered and repeatedly recrystallised from either ethanol, tetrachloromethane, or a mixture of chloroform and ligroin. The pure product, pale yellow needles, melted at 204.5°. The mass spectrum shows the molecular ion at *m/e* 402 and abundant ions at *m/e* 387 ($[M-CH_3]^+$), 325 ($[M-C_6H_5]^+$), 297 ($[M-C_6H_5CO]^+$), 105 (benzoyl ion), and 77 (phenyl ion). These facts indicate that the substance is 3-benzoyl-2,2-diphenyl-4-methyl-2*H*-1-benzopyran. (Found: C 86.30; H 5.59. Calc. for $C_{29}H_{22}O_2$: C 86.54; H 5.51.)

Experiment 2. When the experiment was repeated with the reactants in the ratio 1:2.5 (3.32 g of ethyl 4-methyl-3-coumarincarboxylate, 3.93 g of bromobenzene, and 0.60 g of magnesium), the gas chromatogram showed the presence of biphenyl, unreacted ethyl 4-methyl-3-coumarin-3-carboxylate, a new compound, and 3-benzoyl-2,2-diphenyl-4-methyl-2*H*-1-benzopyran. A sample of the reaction mixture was dissolved in tetrachloromethane, applied on a bentonite column and eluted with tetrachloromethane. Fractions containing pure or almost pure samples of the new compound were combined and the solvent was evaporated. When the residue was treated with ligroin, a substance separated. After repeated recrystallisation from ligroin combined with charcoal treatment, the product melted at 137.5 – 138.5°. The IR spectrum shows two carbonyl peaks (1710 and 1670 cm^{-1}). The most abundant ions in the mass spectrum are the molecular ion at *m/e* 264, and the ions at *m/e* 263 ($[M-H]^+$), 245 ($[M-29]^+$), 187 ($[M-C_6H_5]^+$), 159 ($[M-C_6H_5CO^+]$), 105 (benzoyl ion), and 77 (phenyl ion). These facts indicate that the substance was 3-benzoyl-4-methylcoumarin. (Found: C 77.10; H 4.65. Calc. for $C_{17}H_{12}O$: C 77.26; H 4.58.)

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