ACTA CHEMICA SCANDINAVICA 15 (1961) 1255–1258

The Action of Phenylmagnesium Bromide on Ethyl 3-Coumarincarboxylate

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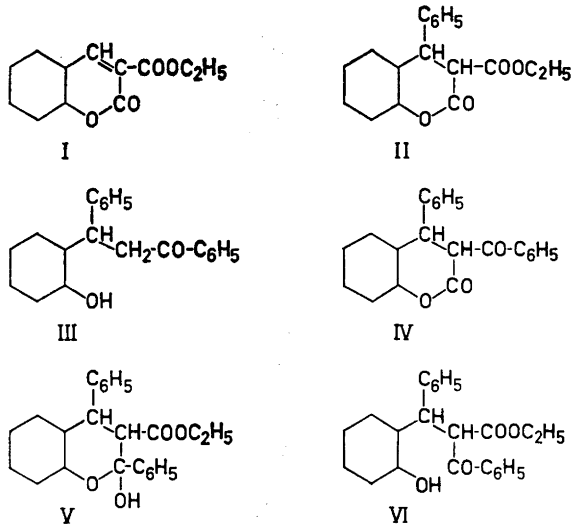
Ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate is formed through 1,4-addition of phenylmagnesium bromide to the conjugated double bond system of ethyl 3-coumarincarboxylate. This rapid reaction is followed by a much slower one in which another molecule of phenylmagnesium bromide reacts with the product of the first reaction.

Reactions between Grignard reagents and different alkylidene and arylidenemalonic esters have previously been investigated in this laboratory. A natural continuation of this work is the study of the reactions between a Grignard reagent and ethyl 3-coumarincarboxylate (I) because this latter substance can be considered an intramolecular arylidenemalonic phenyl ester.

Ethyl 3-coumarincarboxylate was, therefore, brought to react with phenylmagnesium bromide. In the first experiment, in which the molecular ratio of ester and Grignard reagent was 1:2.5, the reaction mixture was worked up after it had been warmed for 15 min. The yield of the main product, ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate (II), was 68.2 %. Owing to the solubility of this substance in ethanol, the rest of it had to be isolated after saponification as 4-phenyl-3,4-dihydrocoumarin; the yield was 9.7 %. Also 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone (III) was isolated from the reaction products of the saponification in a yield of 5.8 %.

However, when, in a second experiment, the reaction product mixture was decomposed after a reaction period of 1.5 h, the yield of the 4-phenyl-3,4-dihydrocoumarincarboxylic ester decreased to 58.4 %, while the yields of 4-phenyl-3,4-dihydrocoumarin and 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone increased to 12.0 and 12.5 %, respectively. When the molecular ratio of ethyl 3-coumarincarboxylate and phenylmagnesium bromide was changed to 1:3.5 and the reaction time increased to 24 h, the respective yields were 38.0, 18.8, and 19.9 %.

Ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate was evidently formed through a 1,4-addition of phenylmagnesium bromide to the conjugated double bond system of ethyl 3-coumarincarboxylate. The substance, which gives



3-(*o*-hydroxyphenyl)-3-phenylpropiophenone on saponification, has apparently its origin in the reaction between phenylmagnesium bromide and the initially formed magnesium compound of ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate. However, this reaction can lead to three compounds, *viz.* 3-benzoyl-4-phenyl-3,4-dihydrocoumarin (IV), ethyl 2-hydroxy-2,4-diphenyl-3-chromanecarboxylate (V), and ethyl *α*-benzoyl-*β*-(*o*-hydroxyphenyl)-*β*-phenylpropionate (VI). It is not possible to state which of them is formed on the basis of the present experimental data.

In order to estimate the lowest extent to which 1,4-addition has occurred in an experiment, the yields of ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate, 4-phenyl-3,4-dihydrocoumarin, and 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone should be summed. Thus, the total yield of the 1,4-addition was about 80 % in each of the three experiments. This reaction is a relative fast one since it went to completion within 15 min.

On the other hand, the yield of 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone in an experiment expresses the extent to which ethyl 3-coumarincarboxylate has reacted with two moles of phenylmagnesium bromide. This value increases slowly with reaction time. This second reaction is, therefore, much slower than the first.

The reaction products were identified by degradation and synthesis. Ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate was transformed into 4-phenyl-3,4-dihydrocoumarin by saponifying it and heating the saponification products for a short time. The identity of the last-mentioned substance was established by its synthesis according to Simpson and Israelstam [1]. Further, when the potassium salt, formed in the saponification, was methylated, dimethyl *o*-methoxybenzhydryl malonate was obtained. By saponification of this substance and decarboxylation of the reaction product, an acid was obtained which was identical with the previously [2] known *β*-*o*-anisyl-*β*-phenylpropionic acid.

3-(Hydroxyphenyl)-3-phenylpropiophenone was converted to 4-phenyl-2-chromene according to Löwenbein, Pongrácz, and Spiess [3] and was also in other respects identical with a sample prepared by the procedure of these authors.

The question whether the 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone is an open ketone or a cyclic semiketal, 4-phenyl-2-chromanol, has not yet been definitely answered. Löwenbein, Pongrácz, and Spiess [3] consider it to be cyclic, whereas Geissman [4] denies this. For the present the author has chosen to call the compound a ketone and hopes to return to the question later.

EXPERIMENTAL

The action of phenylmagnesium bromide on ethyl 3-coumarincarboxylate. A solution of ethyl 3-coumarincarboxylate (10.90 g) in benzene (50 ml) was gradually added to a Grignard reagent prepared from bromobenzene (19.63 g), magnesium (3.00 g), and dry ether (100 ml). The reaction mixture was gently warmed on a water bath for 15 min and then poured into a mixture of hydrochloric acid (30 ml), water (60 ml), and ice (about 200 g). After adding more ether and shaking, the organic phase was separated and washed with water and dilute potassium hydrogen carbonate solution. The acid aqueous phase was extracted once more with ether and this ether was also washed with water and dilute potassium hydrogen carbonate solution before it was combined with the main portion. After drying with sodium sulphate, the ether was evaporated and the residue dissolved in hot ethanol. Ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate (10.10 g) m.p. 101—102° after recrystallization from ethanol, separated on cooling. (Found: C 73.07; H 5.53. Calc. for $C_{18}H_{16}O_4$: C 72.96; H 5.44).

The ethanolic filtrate was evaporated under reduced pressure and the residue (6.81 g) dissolved in ethanol (150 ml). A solution of potassium hydroxide (7.00 g) in water (7 ml) and ethanol (25 ml) was added and the mixture heated on a boiling water bath for 2 h. After the mixture had cooled overnight, the precipitated potassium salt was filtered off and dissolved in water. The solution was acidified with hydrochloric acid and extracted with ether. The ether phase was dried with sodium sulphate and the ether was evaporated. The residue was heated at 160—170° for 10 min and after cooling the substance was treated with ligroin. In this way 4-phenyl-3,4-dihydrocoumarin (1.18 g), m.p. 82—83° after recrystallization from a mixture of benzene and ligroin, was obtained. The substance was identical with a sample prepared according to Simpson and Israelstam [1].

The filtrate, obtained when the potassium salt was separated, was evaporated under reduced pressure and water was added to the residue. The oil that separated was taken up in ether. The solution was dried and the solvent evaporated. The residue was treated with ethanol and the separated crystals (0.87 g) of 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone, m.p. 167.5—168.5° after recrystallization from ethanol, were filtered off. A sample of this ketone was dehydrated to 4-phenyl-2-chromene, m.p. 109—110°, by the method of Löwenbein, Pongrácz, und Spiess [3]. The substance was also in other respects identical with a sample prepared according to the same authors.

When the experiment was repeated but the reaction mixture warmed for 15 min and then kept at room temperature for 1.5 h before it was worked up, the yield of 4-phenyl-3,4-dihydro-3-coumarincarboxylic ester decreased (to 8.65 g) while the yields of 4-phenyl-3,4-dihydrocoumarin and 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone increased (to 1.34 g and 1.88 g, respectively).

When more bromobenzene (27.48 g), magnesium (4.20 g), and dry ether (140 ml) were used in the preparation of the Grignard reagent and the reaction time at room temperature extended to 24 h, the yield of ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate was still lower (5.62 g) and the yields of 4-phenyl-3,4-dihydrocoumarin and 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone were still higher (2.10 g and 3.01 g, respectively).

Saponification of ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate. A sample (3.56 g) of ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate was dissolved in ethanol (80 ml), a solution of potassium hydroxide (3.50 g) in water (3.5 ml) and ethanol (15 ml) was added, and the reaction mixture heated on a boiling water bath for 2.5 h. While the solution was kept in a refrigerator overnight, crystals of a potassium salt separated. The salt was

filtered off and dissolved in water. The aqueous solution was acidified and extracted with ether. The organic phase was dried with sodium sulphate and the solvent evaporated. The residue was heated to 160—170° for 10 min, the melted substance cooled and treated with ligroin. The separated crystals (2.58 g) of 4-phenyl-3,4-dihydrocoumarin, m.p. 82—83° after recrystallization from a mixture of benzene and ligroin, were filtered off.

Ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate (5.44 g) was saponified in ethanol (125 ml) as above with a solution of potassium hydroxide (5.50 g) in water (5.5 ml) and ethanol (15 ml). The precipitated potassium salt was dissolved in water (75 ml) and the solution shaken with dimethyl sulphate (7.00 g) for half an hour. A solution of potassium hydroxide (3.10 g) an water (15 ml) was added and the mixture shaken with dimethyl sulphate (7.00 g) another half an hour. The substance (5.45 g) that had separated during the shaking was filtered off, washed with ether and then dissolved in a large quantity of ether. When the solvent had been partly evaporated, the substance separated again and was filtered off. After another similar treatment, dimethyl *o*-hydroxybenzhydrylmalonate, melting at 113.5—144.5°, was isolated. (Found: C 69.77; H 6.15. Calc. for $C_{19}H_{20}O_5$: C 69.50; H 6.14.)

A solution of potassium hydroxide (3.00 g) in water (3 ml) and ethanol (25 ml) was added to a solution of dimethyl *o*-methoxybenzhydrylmalonate (2.38 g) in ethanol (100 ml) and the mixture heated on a boiling water bath for 3 h. The potassium salt that separated when the reaction mixture was kept overnight in a refrigerator was filtered off and dissolved in water. The aqueous solution was acidified and after some time crystals (1.86 g) of impure *o*-methoxybenzhydrylmalonic acid formed. A sample (1.42 g) of this substance was heated in an oil bath at 190° for 5 min. The residue (1.20 g) was teated with benzene and the precipitated substance, m.p. 132—133°, was filtered off. It was identical with β-*o*-anisyl-β-phenylpropionic acid [2].

The elementary analyses were carried out by Dr. Alfred Bernhardt, Mühlheim.

REFERENCES

1. Simpson, J. D. M. and Israelstam, S. S. *J. S. African Chem. Inst.* **2** (1949) 165 as reviewed in *Chem. Abstr.* **45** (1951) 6196.
2. Holmberg, G. A. *Acta Chem. Scand.* **6** (1952) 421.
3. Löwenbein, A., Pongrácz, E. and Spiess, E. A. *Ber.* **57 B** (1924) 1517.
4. Geissman, T. A. *J. Am. Chem. Soc.* **62** (1940) 1363.

Received February 20, 1961.