

INVESTIGATION OF THE PREPARATION OF 2,4,2',4',2''-PENTAMETHOXY-TRIPHENYLCARBINOL

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2,4,2',4',2''-pentamethoxy-triphenylcarbinol (pentamethoxy red) is an indicator, the colour of which changes from violet to colourless. The colour change occurs in the pH-range from 1.2 to 3.2. Several publications deal with the synthesis of the substances. In all the cases, the preparation is carried out in a nearly identical way [1, 2].

Starting from salicylic-acid, 2-methoxy-benzoic-acid-methylester is prepared in alkaline medium with dimethyl-sulfate in the first step. The second step is the methylation of resorcinol with dimethyl-sulfate, yielding 1,3-dimethoxy-benzene.

This is iodinated in the next step in the presence of acid-binding mercury(II)-oxide in abs. alcohol, to give 2,4-dimethoxy-iodine benzene.

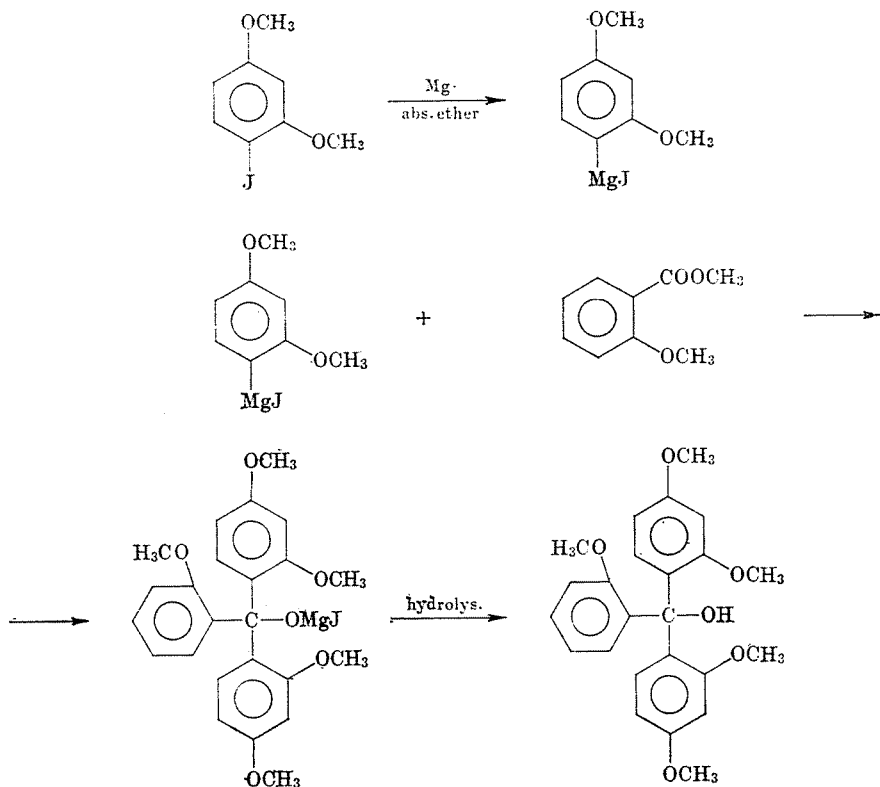
From 2,4-dimethoxy-iodobenzene, 2,4-dimethoxy-phenyl-magnesium-iodide is prepared with metallic magnesium in abs. ether, and the latter is reacted without preparation with 2-methoxy-benzoic-acid-methylester. The end-product is obtained by the hydrolysis of the reaction mixture in the presence of acetic acid (Fig. 1).

This way was followed by LUND [1], further by HOŁOWIECKI et al. [2]. A detailed procedure is given only by the latter. For the two methylation steps, yields of 30 to 35 and 70 to 75 per cent are reported. Iodination is realized with a yield of 40 to 45 per cent, and finally, the most important last step with a yield of 30 to 32 per cent.

In the reproduction of the process described, it was found that in general, yields correspond to the values reported. Only the last step, the Grignard reaction and coupling form an exception, for which only a yield of 5 to 10 per cent could be attained. At such yields, the process is not economical for the industrial production of pentamethoxy red, indeed, referred to resorcinol, a yield of only 2 per cent is attained.

It was thought most important to improve the yields of the rather expensive iodination and of the Grignard reaction and coupling.

Instead of the 50 to 60°C recommended by HOŁOWIECZKI, the preparation of 2,4-dimethoxy-iodobenzene was carried out at room temperature, as recom-



mended by KAUFMANN and KIESER [3]. Even in this case, the yield of 70 per cent, reported by HOŁOWIECZKI, could not be attained with commercial mercury(II)-oxide. On increasing the speed of the agitator, the yield could be increased to 72.2 per cent, when freshly prepared mercuric-oxide was used. When dimethoxy-benzene, recovered in pure form, is also taken into account, this value corresponds to 80.2 per cent, which surpasses even the results of KAUFMANN. At the same time, the regeneration of the very expensive mercuric-oxide has also been solved.

Problems concerning the yield and in close connection with it, production costs and labour demand were met particularly in the last two steps of the synthesis. This can be easily understood from the circumstance that a Grignard excess of 100 per cent is needed for coupling, which means in the case of a 10 per cent yield the complete loss of 95 per cent of the expensive dimethoxy-iodobenzene. The difficulty in the increasing of the yield is the multiple heterogeneity of the reaction, because the Grignard reagent is insoluble in ether. Therefore, several kinds of solvents and solvent mixtures were tried.

When the preparation of the Grignard reagent and coupling were carried out in dialkyl and cyclic ethers or their mixtures in various ratios with benzene

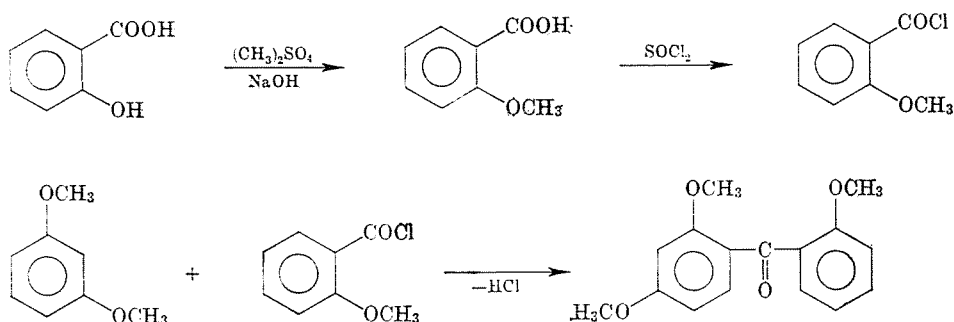
and its alkyl homologues, an important increase in yield could be attained. Depending on the solvent pairs used, the temperature of the reaction was between 45 and 75°C. According to our experiences, an increase in reaction time influenced also favourably the yield.

Particularly good results were attained in the case where the Grignard reagent was prepared in abs. alcohol, and the coupling component, 2-methoxybenzoic-acid-methylester, was added in form of solution in abs. benzene to the reaction mixture.

When coupling was carried out in a 1 : 1 ether-benzene mixture at the boiling point, i.e. 55 to 57°C, after a reaction time of 3 hours pentamethoxy red could be prepared at a yield of 72 per cent. The new pair of solvents, the higher temperature and longer reaction time doubled thus the yield.

In addition to this substantial improvement of the process, described in the literature, a novel and even more economical way of synthesis has been developed.

Starting from salicylic-acid, 2-methoxy-benzoic-acid has been prepared with dimethyl-sulfate, which was converted with thionyl-chloride into 2-methoxybenzoyl-chloride, and this was used for the acylation of 1,3-dimethoxybenzene. 2,4,2'-trimethoxy-benzophenone was obtained in a quick reaction at a good yield (Fig. 2).

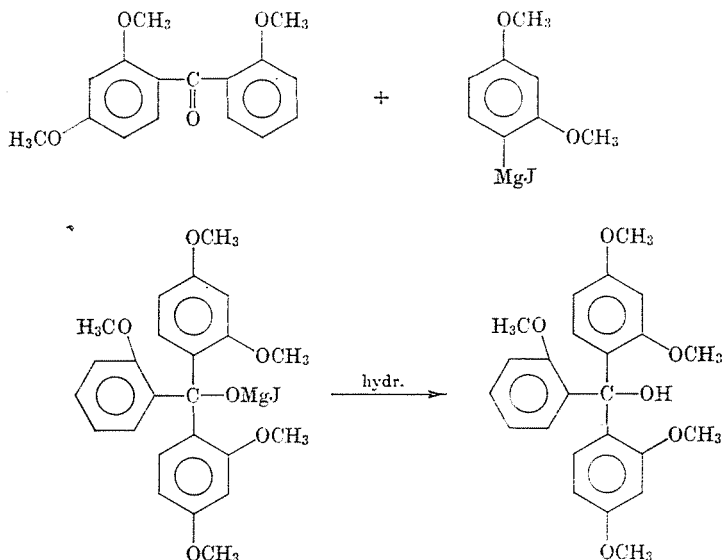


This was reacted in ether-benzene solution in the way described above with the Grignard compound of 2,4-dimethoxy-iodobenzene. By the acetic-acid hydrolysis of the reaction mixture, the end product could be obtained at a yield of 65 per cent (Fig. 3).

2,4-dimethoxy-iodobenzene and the Grignard compound were prepared also for this kind of reaction in the way as described above.

The advantage of our process over the syntheses known so far is that it involves a substantially lower consumption of the costly and labour exacting 2,4-dimethoxy-iodobenzene. While in the first technology four moles of

2,4-dimethoxy-iodobenzene are needed for the preparation of one mole of pentamethoxy red, only two moles are requested in our new process. In addition, it is worth to mention that the quality characteristics of the products synthesized by us according to both technologies were superior to those of the commercial products.



Experimental part

1. Preparation of 2,4-dimethoxy-iodobenzene

To a mixture of 100 g (0.725 mole) of dimethoxy-benzene and 380 ml of abs. alcohol a mixture of 200 g (0.79 mole) of finely ground iodine and 160 g (0.74 mole) of pulverized mercury(II)-oxide is added in small portions, under vigorous stirring, at room temperature, waiting after the addition of each portion until the colour of iodine disappears. This operation requires about 7 hours. To ensure complete reaction, the mixture is stirred for further 5 hours. The precipitate is filtered and washed with 2×150 ml portions of hot abs. alcohol.

The combined filtrate is evaporated under vacuum. The residue is a yellow oil, from which a small amount of mercury(II)-iodide separates after cooling. The residue is dissolved in 800 ml of ether, extracted with 3×100 ml portions of a 2 per cent NaOH solution, washed with water, until it becomes neutral

and dried over sodium sulfate. Ether is distilled off, and the residue is fractionated under vacuum. 138 g of product is obtained.

B.p.: 161–166°C/14 mm Hg.

Yield: 72.2 per cent.

2. Preparation of 2,4,2',4',2''-pentamethoxy-triphenylcarbinol

Under dry conditions, a few pure iodine crystals are added to 6 g (0.257 mole) of Mg chips, washed freshly with ether and dried under vacuum, and the flask is cautiously heated, until it is filled with iodine vapours. A solution of 62 g (0.235 mole) of freshly distilled 2,4-dimethoxy-iodobenzene in 300 ml of abs. ether is added to the content of the flask. Start of the reaction is indicated by the turbidity of the solution. The reaction mixture is boiled for 2 hours on a water bath. The predominant part of Mg is dissolved, and the Grignard reagent formed appears as a brownish-green oily phase in the system.

During boiling, the solution of 9.6 g (0.058 mole) of 2-methoxy-benzoic-acid-methyl-ester in 300 ml of abs. benzene is added drop by drop to the oily emulsion. During the dropwise addition, a viscous, dark oily phase forms, which is solved upon further 3 hours of boiling.

After heating is off, the reaction mixture is cooled, and under continuous cooling with ice, 200 ml of 10 per cent acetic acid is added dropwise below at 10°C. After half an hour of further mixing, the organic phase is separated, washed with 3×100 ml of 2 per cent Na_2CO_3 solution and water, until it becomes neutral, and dried over Na_2SO_4 . Ether and benzene are evaporated on a water bath. A viscous, dark-yellow oil is obtained, which crystallizes after cooling and a short time of rest. The crystals are triturated with a double amount of isopropyl-alcohol and filtered, then washed with a small amount of isopropyl-alcohol and dried.

17.1 g of product is obtained.

M.p.: 138 to 141°C.

Yield: 71.8 per cent.

3. Preparation of 2-methoxy-benzoic-acid

To a solution of 100 g (0.725 mole) of salicylic-acid and 72 g (1.8 mole) of sodium-hydroxide in 600 ml of water, 126 g (1 mole) of dimethyl-sulfate is added. The reaction mixture is vigorously agitated for 15 minutes, then heated to the boil. Further 30 g (0.75 mole) of sodium-hydroxide is added in form of a concentrated solution, and the mixture is boiled for 6 hours to complete the reaction.

After cooling, the mixture is acidified with conc. hydrochloric-acid. The precipitate formed is filtered off, washed with water and dried. This 2-methoxy-

benzoic-acid contains salicylic-acid impurity. To remove the salicylic-acid, the product is boiled for 1 hour with concentrated slacked lime. Calcium-salicylate is insoluble. After filtration, the solution is acidified again, and a product free of salicylic-acid is obtained.

78.2 g of 2-methoxy-benzoic-acid is formed.

B.p.: 96–99°C.

Yield: 71 per cent.

4. *Preparation of 2-methoxy-benzoyl-chloride*

To 200 g (1.68 mole) of thionyl-chloride 60.8 g (0.4 mole) of 2-methoxy-benzoic-acid is added in several portions. This is immediately dissolved, and the liberated hydrochloric-acid and sulfur-dioxid gases bring the solution to the boil. After the gas evolution ended, the reaction mixture is boiled for 30 minutes.

The excess of thionyl-chloride is distilled off and the residue is fractionated under vacuum.

62 g 2-methoxy-benzoyl-chloride is obtained.

Bp.: 142 to 143°C/17 mm Hg.

Yield: 91 per cent.

5. *Preparation of 2,4,2'-trimethoxy-benzophenone*

To 85 g (0.5 mole) of 2-methoxy-benzoyl-chloride 120 g (0.87 mole) of 1,3-dimethoxy-benzene is added. The reaction mixture is heated cautiously to the boil. Under vigorous evolution of hydrochloric-acid gas, a violent reaction begins. Boiling is continued for about 1 hour, until the evolution of hydrochloric-acid gas has stopped. The excess 1,3-dimethoxy-benzene (about 50 g) is distilled off, and the residue is fractionated under vacuum.

110 g of 2,4,2'-trimethoxy-benzophenone is obtained.

B.p.: 200 to 210°C/0.5 mm Hg.

Yield: 81 per cent.

6. *Preparation of 2,4,2',4',2''-pentamethoxy-triphenylcarbinol by a new synthesis*

Starting from 6 g (0.257 mole) of magnesium and 62 g (0.235 mole) of 2,4-dimethoxy-iodobenzene, the Grignard reagent is prepared according to Paragraph 2.

Under boiling, the solution of 34 g (0.125 mole) of 2,4,2'-trimethoxy-benzophenone in 300 ml of abs. benzene is added dropwise to the oily emulsion. During this dropwise addition, a viscous, dark, oily phase is formed, part of

which is solvated by further 3 hours of boiling. After heating is off, the reaction mixture is cooled, and under continuous cooling with ice, 200 ml of 10 per cent acetic-acid solution is added below 10°C. Further processing is carried out as described in Paragraph 2.

33.6 g of product is obtained.

M.p.: 138 to 141°C.

Yield: 65.6 per cent.

Summary

At the Department of Organic Chemical Technology of the Technical University, Budapest, the laboratory synthesis of 2,4,2',4',2''-pentamethoxy-triphenylcarbinol, known from the literature, has been developed into a technology, suitable for industrial production.

The yield of the steps, critical from technological and economic points of view, has been increased to more than twofold. At the same time, a completely novel, improved route of synthesis has been developed for the preparation of the product.

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