

Synthesis of Some Substituted Analogues of Natural Flavones and Chalcones

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Abstract--Using modified methods, we synthesized some substituted analogues of natural flavones with the formation of a chromon system (method A using DMSO in the presence of copper (II) bromide and method B in the presence of copper (II) chloride), as well as chalcones using the Kleisen-Schmidt method and the use of phenylacetic acid. Some physicochemical constants of the synthesized compounds are given, structures on the PMR spectrum and Tesla BS-567A are established, the crystallographic parameters of single crystals are determined and refined on a «Xcalibur» CCD diffractometer, which may make it possible to obtain compounds with useful biological properties for further use them in chemical modification.

Keywords--synthesis, flavones, chalcones, structures, crystallographic parameters.

I. INTRODUCTION

The beneficial properties of natural and synthetic flavones and chalcones [3], which have prospects for medical use, prompted us to undertake a search for suitable and effective methods for the preparation of these compounds. They are a fertile object for chemical modification and further practical use as starting materials. To this end, we have developed methods for the synthesis of certain substituted analogues of natural flavones and chalcones.

II. APPLIED MATERIALS AND RESEARCH RESULTS

Considering the results of studies [3], for the synthesis of analogues of natural flavones and chalcones, 2'-hydroxychalcones **3a-d** were used as the most accessible, starting compounds for constructing the chromon system.

The starting ketones **3a-d** were obtained by the well-known Kleisen-Schmidt method as a result of alkaline condensation of substituted 2-hydroxyacetophenones with the corresponding heterocyclic aldehydes.

One of the most commonly used methods for producing flavones is the oxidative cyclization of 2'-hydroxychalcones with various oxidizing agents.

Earlier in [1], the oxidation of chalcones with dimethylsulfoxide (DMSO) was carried out in the presence of catalytic amounts of iodine with the formation of the corresponding flavones.

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So, for the synthesis of substituted flavones, we proposed a modified version using DMSO in the presence as a catalyst of copper (II) bromide according to method A and copper (II) chloride according to method B. The application of these methods according to method A and B to ketones **3a-d** led to the formation of the chromon system of 3-unsubstituted flavones **4a-c**.

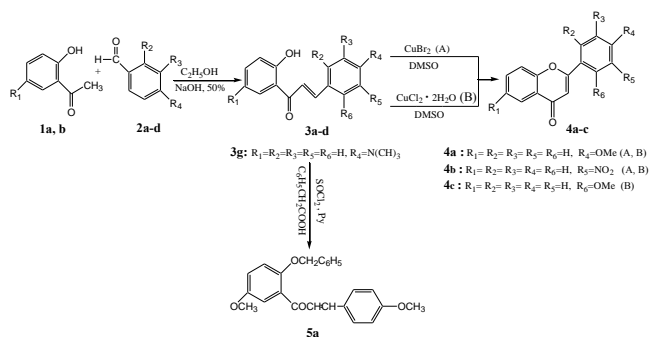
The role of the oxidizing agent in these reactions is played by atmospheric oxygen. The high temperature of the solvent and alkaline environment favor the rapid oxidation of chalcone to flavon. In this regard, this feature of the course of synthesis in the presence of atmospheric oxygen can be used as a peculiar way to obtain flavon without isolation of intermediate products.

The synthesized flavones **4a-c** are colorless crystalline substances that are readily soluble in most organic solvents, but insoluble in water, are easily detected by blue or violet fluorescence in UV light (Table 1).

Thus, the methods A and B developed by us are one-stage methods for producing flavones without the formation of by-products and reducing the duration of the process. These methods have theoretical implications. However, the difference in the yields of products is revealed (Table 1). Compound **4a** by method B has a higher yield than by method A, and compound **4b** by method A has a higher yield than by method B.

The use of phenylacetic acid in pyridine and thiosulfate chloride allows the synthesis of a new substituted chalcone **5a** [2].

The obtained chalcones **3g** and **5a** - crystalline substances of yellow or pale yellow color, readily soluble in most organic solvents, but not soluble in water, are easily detected by yellow fluorescence in UV light (Table 1).



III. EXPERIMENTAL PART

The reaction progress and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates in benzene: ethanol (9: 1) systems for flavone compounds and in benzene for chalcone compounds.

The melting point was determined on a device for determining the melting point (PTP). Crystals **3g**, **4c**, **5a** were grown from a solution in isopropanol at room temperature. The crystallographic parameters of single crystals were determined and refined on a "Xcalibur" CCD diffractometer. The structure of compounds **4a**, **b** was determined on a Tesla BS-567A instrument in $CDCl_3$.

The table below shows some physicochemical constants of the synthesized compounds.

Table 1

No	Compound	Mp, °C	Gross formula	Ways	Exit, %	Rf
1	3g	160-170	C ₁₇ H ₁₇ O ₂ N	-	47	0,25**
2	4a	153-155	C ₁₆ H ₁₁ O ₃	A	20	0,50*
				B	46	
3	4b	200-250	C ₁₅ H ₉ O ₄ N	A	43	0,40*
				B	28,4	
4	4c	100-110	C ₁₆ H ₁₂ O ₃	B	26,5	0,47*
5	5a	130-140	C ₂₄ H ₂₂ O ₄	-	25	0,66**

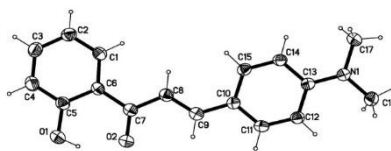
* benzene: ethanol (9: 1)

** benzene

General procedure for the preparation of starting compounds 3a-d.

To a solution of 20 mmol of compound 2-hydroxyacetophenone **1a, b** in 25 ml of ethanol was added 20 mmol of the corresponding aldehyde **2a-d**. 4.7 ml of a 50% NaOH solution were added to the warm solution. Constantly mixed until precipitation. Then the precipitate was suspended with ethanol ~ 15-20 ml to a homogeneous medium, kept at room temperature for 20 hours and acidified to a neutral reaction with a 20% solution of acetic acid. The precipitate was filtered off and crystallized from isopropyl alcohol.

Crystals **2'- Hydroxy-4-dimethylaminochalcon (3g)** monoclinic, $a=12.156(2)$ Å, $b=10.277(1)$ Å, $c=12.503(2)$ Å, $\beta=115.79(2)^\circ$, $V=1406.4(4)$ Å³, $M=265,30$, $Z=4$, $D_{\text{calc.}}=1.25$ g/cm³, pr. gr. P2₁/c, $R=0.049$ for 1322 reflections. Non-hydrogen atoms of the molecule are located in approximately the same plane; this state is stabilized by the intramolecular H-bonds O1-H ... O2.



The general procedure for producing flavones 4a, b by method A.

To a solution of 10 mmol of the corresponding chalcone **3a, b** in 20 ml of DMSO was added 2 g of copper (II) bromide. The reaction mixture was boiled for 2 hours and diluted with distilled water. The precipitate was filtered and crystallized from ethyl acetate.

In the PMR spectrum (CDCl₃) of the substance **3-H-4'-methoxy flavone(4a)** at 3.8 ppm. An intense narrow singlet of the oxymethyl group is observed. A group of signals in the field of a weak field of 6.2-8.3 ppm refers to aromatic protons, of which individually it is possible to isolate the H-3 singlet at 6.70 ppm, the proton doublet H-3' and H-5' at 7.0 ppm and a doublet of protons H-2' and H-6' at 7.82 ppm. Due to the mutual overlap and second-order effects, the signals of the remaining aromatic hydrogens cannot be individually assigned, but the integration of the

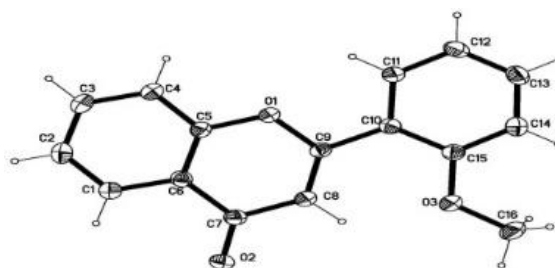
spectrum of this region shows the presence of nine aromatic hydrogens. Thus, the qualitative and quantitative analysis of the spectrum corresponds to structure **4a**.

In the PMR spectrum (CDCl_3) of the 3-H-5'-nitroflavone substance (**4b**), the positions of the H-3 signals (7.9 ppm) and H-6' (8.75 ppm) can be assigned. The signals of the other aromatic protons of cycles A and B are located in the region of 8.5 and 7.25 ppm. Integration of the spectrum shows that the signals of seven protons are located in this region of the spectrum, which corresponds to structure **4b**.

The general procedure for preparing flavones 4a-b according to method B.

To a solution of 10 mmol of the corresponding chalcone **3a-b** in 20 ml of DMSO was added 2 g of aqueous copper (II) chloride. The reaction mixture was boiled for 2-5 hours and diluted with distilled water. The precipitate was filtered and crystallized from an appropriate solvent.

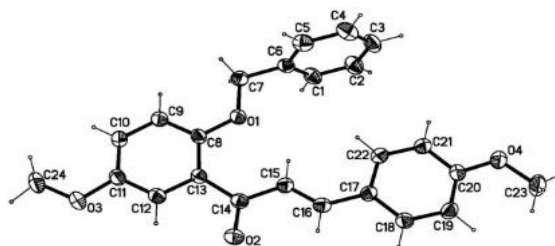
Crystals 3-H-6'-methoxyflavone (**4c**) monoclinic, $a=7.3022(6)$ Å, $b=8.3292(6)$ Å, $c=10.823(1)$ Å, $\alpha=97.801(7)^\circ$, $\beta=92.841(7)^\circ$, $\gamma=111.171(7)^\circ$, $V=604.69(9)$ Å³, $M=252.26$, $Z=2$, $D_{\text{calc.}}=1.385$ g/cm³, pr. gr. P-1, $R=0.086$ for 1729 reflections. Non-hydrogen atoms of the molecule are in the same plane.



The method of obtaining 5', 3-dimethoxy-(2'-oxomethylphenyl) chalcone 5a.

A mixture of 10 mmol of the corresponding chalcone **3d**, 10 mmol of phenylacetic acid and 20 ml of pyridine was stirred, 2 ml of SOCl_2 was added dropwise. The mixture was boiled for 1 hour while stirring. After cooling, 5 ml of a 1% HCl solution was added. Then it was washed with 1% Na_2CO_3 solution and washed again with distilled water. The precipitate was crystallized from ethanol.

The crystals of the new derivative of chalcone **5a** are rhombic, $a=7,263(2)$ Å, $b=12,825(2)$ Å, $c=21,031(3)$ Å, $V=1959.3(5)$ Å³, $M=374,42$, $Z=4$, $D_{\text{calc.}}=1.27$ g/cm³, pr. gr. $P2_12_12_1$, $R=0.0351$ for 1792 reflections. The atoms of the initial chalcone are in the same plane, and the plane of the atoms of the substituted phenyl ring is perpendicular to the original plane.



IV. CONCLUSION

So, using the modified method, we obtained a new 2'-substituted chalcone **5a**. The key compound 2'-hydroxychalcone **3g** was also obtained for the further synthesis of analogues of natural flavonoids.

The reactions carried out once again showed that flavonoids are a fertile object for chemical modification and their practical use as starting materials.

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