SIMPLE AND EFFECTIVE SYNTHESIS OF ISOFLAVONES AND 3-ARYLOXYCHROMONES

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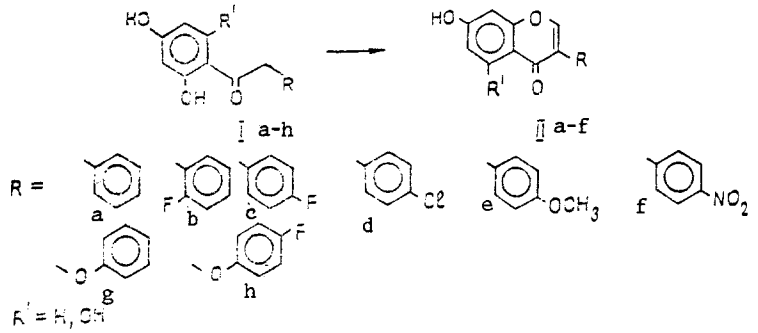
Conditions have been developed for an effective synthesis of 7-hydroxy- and 5,7-dihydroxyisoflavones and also of 3-aryloxy-7-hydroxychromones. The disadvantages and advantages of alternative pathways for the synthesis of these compounds are discussed. The proposed method of synthesis permits considerable simplification of the preparation of compounds of these series.

The search for new highly effective drugs among modified analogues of isoflavones is extremely promising. The broad spectrum of therapeutic action with low toxicity and the availability of a number of natural representatives of the isoflavones has made their use in medical practice possible [1]. Together with drugs from natural raw materials [2], synthetic products are acquiring ever greater importance. Among the latter, practical interest is presented by phenoxychromones, which possess a well-defined cholagogic action [3]. In this connection, we have undertaken attempts to develop a convenient and effective method of obtaining compounds based on 7-hydroxychromone containing an aryl or aroxyl fragment in position 3.



The starting materials in the synthesis of the desired chromones were α-aryl- and α-aryloxyacetophenones (Ia-h), obtained by the condensation of resorcinol or phloroglucinol with the appropriate acetonitriles under the conditions of the Houben–Hoesch reaction [4].

The most convenient cyclizing agent for the conversion of α-aryl-2-hydroxyacetophenones into isoflavones is acetic formic anhydride [5, 6]. By using it in combination with triethylamine, the most effective catalyst of the reaction, we obtained the isoflavones (IIa-f) with high yields from the ketones (Ia-f) (Table 1). However, it was impossible to obtain the aryloxychromones (IIg and h) by this method. According to TLC results, under the influence of triethylamine the exhaustive formylation of the hydroxy groups of the aryloxyacetophenones (Ig and h) by the acetic formic anhydride took place. This was shown by the fact that 15-30 min after the beginning of the synthesis not one of the substances present in the reaction mixture gave a coloration with an ethanolic solution of ferric chloride. After the completion of the synthesis, as shown by TLC, the reaction mixture consisted of 10-30% of the chromones and 70-90% of the initial ketones. Consequently, in the second stage of the reaction the fully formylated acetophenone (III) was, in the main, deformylated, producing the initial α-aryloxyacetophenone (I), and only a small part of it was converted into the chromone (II).

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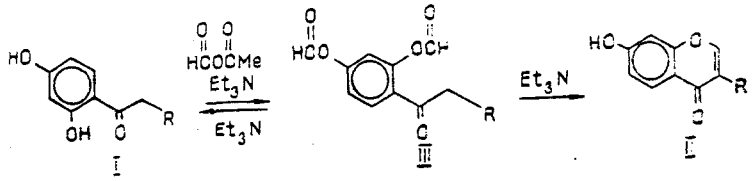
TABLE 1. Conditions of Preparation and Yields of Isoflavones and 3-Aryloxychromones

Compound	Yield, %		mp, °C	Literature
	Acetic formic anhydride	Vilsmeier reagent		
IIa	91	98.5	213–215	5
IIb	90	96.2	223–224	6
IIc	93	97.3	249–250.5	6
IId	97	95.9	261.5–262	6
IIe	99	98.1	257–258	5
IIf	99	97.4	211.5–213	6
IIg*	99	97.6	292–293	5
IIh*	20	97.0**	213–214	
	15	95.7	234–5	

*The results of elementary analysis for (IIg) and (IIh) agreed with the calculated figures.
**Yield with the use of methanesulfonyl chloride – 75%; with phosphorus trichloride – 97%; with phosphorus oxychloride – 96.5%; with phosphorus pentachloride – 96.7%; with thionyl chloride – 85.5%.



In the synthesis of the isoflavones (IIa-f) a different pattern was observed: Practically all the formyloxyacetophenone (III) was converted into the isoflavone and only 1-3% of it was deformylated, giving the initial α-arylacetophenone.

This difference in the behavior of the O-formylated α-aryl- and α-aryloxyacetophenones can be explained by the dissimilar acidities of the protons of their α-methylene units and, as a consequence, the different rates of transformation into chromones [5, 7]. Since the rate of deformylation of compounds (III) was the same but the rate of heterocyclization was considerably higher in the α-arylketones (IIIa-f), for the latter of the two competing reactions heterocyclization predominated, while for the α-aryloxyketones (IIIg, h) it was deformylation that predominated. Consequently, the conditions described in [5] are unstable for the synthesis of 3-aryloxychromones.

The method of Hungarian scientists [8], consisting of the action on the corresponding 2-hydroxyacetophenone of methyl formate and sodium tert-butanolate with subsequent treatment of the reaction mixture with an acid, proved to be unsuitable for obtaining hydroxylated 3-aryloxychromones. Again, hydroxyisoflavones were obtained with only low yields by this method [1].

Our attempt to obtain the aryloxychromone (IIh) by Venkataraman's orthoformate method [9] proved unsuccessful. Under the conditions of this reaction, as TLC showed, there was intensive resinification of the reaction mixture and the desired chromone was formed in only insignificant amounts.

A method for obtaining isoflavones consisting in the action of the Vilsmeier reagent on trifluoroborate complexes of the corresponding α-arylketones is widely known [1, 10, 11]. The Vilsmeier reagent is prepared beforehand by mixing dimethylformamide with an equimolar amount of methanesulfonyl chloride. Only one 3-aryloxychromone has been obtained under such conditions [10].

In the experiments we found that the procedure for obtaining chromones can be substantially simplified without any complications whatever in relation to the desired products.