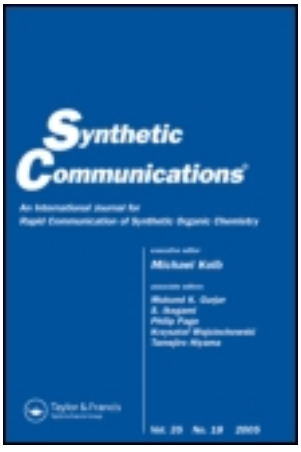

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New Convenient Synthesis of Homoisoflavanones and (±)-Di-O-methyldihydroeucomin

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New Convenient Synthesis of Homoisoflavanones and (±)-Di-O-methyldihydroeucomin

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Abstract: Upon reaction of 1-(2-hydroxyphenyl)-3-phenylpropane-1-ones (2′-hydroxydihydrochalcones) with dimethylaminodimethoxymethane in boiling toluene, the corresponding 3-benzylchromones are obtained in excellent yields. These latter lead to 3-benzylchroman-4-ones (homoisoflavanones) by catalytic hydrogenetion. These reactions were applied to the synthesis of (±)-3-benzylchroman-4-one and (±)-3-(4-methoxybenzyl)-5,7-dimethoxychroman-4-one, (±)-di-O-methyldihydroeucomin.

Keywords: 3-Benzylchromones, homoisoflavanones, (±)-di-O-methyldihydroeucomin

INTRODUCTION

Homoisoflavonoids were isolated from Eucomis species: E. bicolor, E. autumnalis, E. punctata[1–5] and Ophiopogonis japonicus[6,7] belonging to the Liliaceae family. The interest in this field continued with the isolation of novel derivatives presenting various hydroxy(methoxy) substitution patterns.[8–10]

With the exception of Brazilin, Hematoxylin, and Scillascillins, the homoisoflavanones constitute a homogenous group of naturally occurring oxygen heterocyclic compounds and correspond to the biogenetically and structurally related 3-benzylidenechroman-4-ones **1**, 3-benzylchromones **2**,

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3-benzylchroman-4-ones **3a** and 3-benzyl-3-hydroxy-chroman-4-ones **3b** (Fig. 1).[11]

Besides their phytochemical importance and as for the case of flavonoids, these derivatives display various biological properties. For instance, 3-benzylidene-chroman-4-ones, inhibit the growth, the sporogenesis and the enzymes involved in the infection mechanism of Phytophtora parasitica[12] and present antifungal activity.[13] Some substituted 3-benzylidene-chroman-4-one display anti-inflammatory, analgesic, platelet anti-aggregating,[14] and hypocholesterolemic activites.[15] On the other hand, various 3-benzylchromones possess angioprotective, antiallergic, antihistaminic properties[16] and some natural derivatives display antimutagenic,[17] phosphodiesterase isoenzyme-inhibiting[18] and antiviral properties.[19,20]

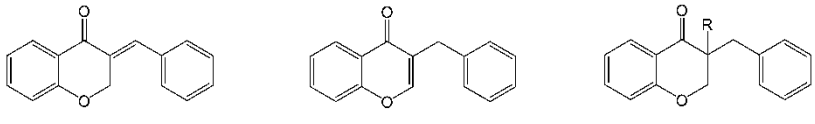
During the course of a research program in connection with the preparation of potential therapeutical agents, we had the requirement of large amounts of 3-benzyl-chromones. An extensive survey of the literature indicated that 3-benzyl-chromones may be obtained by the following procedures:

From 3-benzylidenchroman-4-ones by the isomerisation of their exocyclic double bond into the pyrone ring, under the influence of potassium tert-butyrate,[4] rhodium trichloride[21] or Raney nickel.[22] These reactions lead generally to low yields and/or to mixtures.

By cyclization of conveniently substituted 1,3-diphenylpropane-1-ones (2′-hydroxydihydrochalcones) using ethylformate and sodium[23,16] or a mixture of dimethylformamide, boron trifluoride and methanesulfonyl chloride.[24] Although these methods lead to the expected derivatives, they did not prove to be satisfactory for our needs of large-scale preparations.

In the case of 3-benzylchroman-4-ones, their preparation is limited by the availability of the starting 3-benzylchromones. These latter are obtained with low yields by direct cyclization of 2′-hydroxydihydrochalcones with paraformaldehyde in basic media,[25] by hydroboration followed by chromic acid oxidation of 3-benzyl-4-hydroxy-coumarins[26] or 3-benzylidene-chroman-4-ones.[27]

The availability of new convenient routes for the synthesis of these derivatives would thus be interesting. Therefore, we investigated the elegant chromone synthesis described by Fohlisch, in which a suitable 2′-hydroxy-acetophenone is condensed with dimethylaminodimethoxymethane to form the corresponding enaminoketone, which is cyclized further to the



1 2 **3a: R = H** **3b: R = OH**

Figure 1. Reference compounds.

corresponding chromone in acidic media.[28] This method was applied further to the preparation of isoflavones from 2′-hydroxydeoxybenzoins.[29]

RESULTS

Our method follows the same design as these chromone preparations and results from the condensation of suitable 1,3-diphenyl-propane-1-ones.[16] (2′-hydroxydihydrochalcones) with dimethylaminodimethoxymethane, a one-carbon unit molecule. However, in our experiments, when the reaction was performed with the various substituted derivatives **4a-g** in boiling toluene, the expected enaminoketones were not isolated and the unexpected 3-benzyl-chromones **5a-g** were obtained directly in excellent yields (Scheme 1).

Table 1 shows the physicochemical data related to the prepared 3-benzylchromones **5a-g.** Their structure was established by elemental analysis, infrared (v C = 0: 1640 cm − 1), ^{1}H and ^{13}C NMR spectroscopy,[30] melting point and mixed melting point with our previously prepared reference samples.[16]

The synthesis of 3-benzylchroman-4-ones was achieved in the case of (±)-3-benzylchroman-4-one **6a** and (±)-3-(4-methoxybenzyl)-5,7-dimethoxychroman-4-one, (±)-di-O-méthyldihydroeucomin **6f**, via the catalytic hydrogenation of the corresponding 3-benzylchromones **5a** and **5f** (Scheme 2). The structure of these derivatives was confirmed by elemental analysis, infrared, melting point, and mixed melting point with reference samples.[4,25–27] The overall yields of the homoisoflavanones prepared by these routes are higher than those obtained with the previously described procedures.

In conclusion, this study indicates that it is now possible to prepare conveniently the 3-benzylchromones and the 3-benzylchroman-4-ones (homoisoflavanones) in excellent yields.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 177 spectrophotometer and ^{1}H NMR spectra on a Varian T 60 spectrometer. Glass equipment was dried at 100°C in an oven prior to use.

General Procedure for Compounds 5a–g

3-(3,4-Dimethoxybenzyl)chromone **5e**

In a dry round-bottom flask, equipped with a magnetic stirring bar and a reflux condenser topped with a calcium chloride drying tube, 1-(2-hydroxyphenyl)-3-(3,4-dimethoxy-phenyl)propane-1-one **4e** (2′-hydroxy-3,4-dimethoxydihydrochalcone) (2.86 g, 10 mmoles), dimethylaminodimethoxymethane (1.45 g,

4a-g **5a-g**

4a, 5a : $R^1 = R^2 = R^3 = R^4 = H$
4b, 5b : $R^1 = OCH_3$; $R^2 = R^3 = R^4 = H$
4c, 5c : $R^1 = R^2 = R^3 = H$; $R^4 = OCH_3$
4d, 5d : $R^1 = R^2 = H$; R^3- $R^4 = O\text{-}CH_2\text{-}O$
4e, 5e : $R^1 = R^2 = H$; $R^3 = R^4 = OCH_3$
4f, 5f : $R^1 = R^2 = R^4 = OCH_3$; $R^3 = H$
4g, 5g : $R^1 = R^2 = R^3 = H$; $R^4 = Cl$

Scheme 1. Synthesis of 3-benzylchromones.

Table 1. Physico-chemical data of 3-benzylchromones

Product	Molecular formula	Reaction time	Yield (%)[a]	m.p.°(C) (ethanol)[b]	Litt. m.p.°(C)
5a	$C_{16}H_{12}O_6$	5 h	94	109–110	110[16,23]
5b	$C_{17}H_{14}O_3$	5 h	95	130	131[16]
5c	$C_{17}H_{14}O_3$	5 h	97	100	101[16]
5d	$C_{17}H_{12}O_4$	5 h	92	102–104	104[16]
5e	$C_{18}H_{16}O_4$	6 h	91	114	115[16]
5f	$C_{19}H_{18}O_5$	6 h	95	113	114[16]
5g	$C_{16}H_{11}O_2Cl$	6 h	94	140	140[16]

[a]All yields in isolated products.
[b]m.p. (uncorrected); mixed m.p. with reference samples not depressed.

12 mmoles), and dry toluene (150 ml) were refluxed during 5 h (the progress of the reaction is monitored by tlc). When all the starting products have reacted, the solvent is evaporated to give 2.87 g (97%) of pure 3-(3,4-dimethoxybenzylchromone **5e** m.p. 102–103°C (ethanol).

Preparation of 3-Benzylchromones **5a–d** and **5f–g**

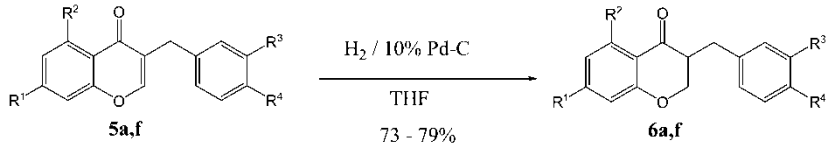
All reactions are performed from the corresponding 2′-hydroxydihydrochalcones **4a–d** and **4f–g** according to the same procedure.

Products, yields and physico-chemical data are reported in Table 1.

General Procedure for Compounds 6a, 6f

(±)-3-(4-Methoxybenzyl)-5,7-dimethoxychroman-4-one: (±)-di-O-méthyldihydroeucomin **6f**

A solution of 5,7-dimethoxy-3-(4-methoxybenzyl)-chromone **5f** (326 mg, 1 mmol) in THF (50 mL) containing a pinch of 10% PD/C catalyst, is



5a,6a : $R^1 = R^2 = R^3 = R^4 = H$ **5f,6f** : $R^1 = R^2 = R^3 = R^4 = OCH_3$

Scheme 2. Synthesis of 3-benzylchroman-4-ones.

hydrogenated (1 atm) at r.t. until hydrogen (27 mL,1.2 mmol) was absorbed. The reaction mixture is filtered and the solvent evaporated. The residue is purified by column chromatography over silica gel (eluent: ethyl acetate-petroleum ether 3–2). The crude product was recrystallized from petroleum ether to give pure (±)-di-O-méthyldihydroeucomin **6f**, mp 83°C; Litt. 82–84°C.[4] Yield 259 mg (79%).

This compound has the same IR spectrum as a reference sample and its mixed melting point with the reference sample is not depressed.[4]

(±) 3-Benzylchroman-4-one **6a**

The synthesis of this compound was achieved with the same procedure, via the catalytic hydrogenation of the 3-benzylchromone **5a**. m.p. 63°C; Litt. 62–64°C;[26] yield 73%. This compound has the same IR spectrum as a reference sample, and its mixed melting point with the reference sample, is not depressed.

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