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# A New Route for the Synthesis of 5-Methoxychroman-3-one

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## A NEW ROUTE FOR THE SYNTHESIS OF 5-METHOXYCHROMAN-3-ONE

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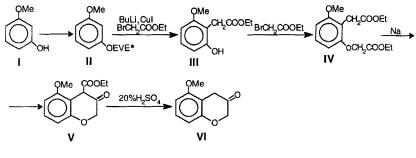
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ABSTRACT: 2'-Hydroxy-6'-methoxyphenylacetic acid ethyl ester was obtained in two steps in 86% yield via intermediate formation of organocopper complex. A possible application of this reaction is the simplification of the synthesis of 5-methoxychroman-3-one.

Chroman-3-ones are important intermediates for the preparation of different potentially biologically active compounds<sup>1,2,3</sup>. All available routes for the preparation of these products are summarized in the article by Danan and Kirkiacharian<sup>4</sup>, where the authors come to the conclusion that there is not general and simple way for the preparation of the chromanones.

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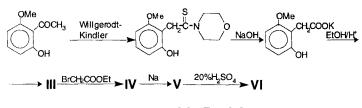
In this paper we report the direct synthesis of 2'-hydroxy-6'methoxyphenylacetic acid ethyl ester which allows 5-methoxy-chroman-3-one to be synthesized in five steps from commercially available 3methoxyphenol (Scheme 1):



\*EVE=CH3-CH-O-CH2CH3

#### **SCHEME 1.**

After successful synthesis of 2'-hydroxy-6'-methoxyacetophenone<sup>5</sup> we continued our work for the preparation of 5-methoxychroman-3-one in two directions: reproduction of the reactions<sup>6,7</sup> in Scheme 2 and direct synthesis



#### **SCHEME 2.**

of III using EVE-protected 3-methoxyphenol selectively litnated at 2-position and the ethyl ester of bromacetic acid as an electrophile. The <sup>1</sup>H-NMR spectrum of the product in this experiment showed unequivocally methylation at the desired position: singlet at 3.75 ppm due to the methylene protons next to phenyl ring and an ester group triplet at 1. 2-1.35 ppm for the methyl and a quartet at 4. 1-4. 25 ppm for the methylene protons, as well as the signals due to the 3-methoxyphenol. The same signals were present in the spectrum of III synthesized as shown in Scheme 2. When the reaction was performed in the presence of 0.5 mol CuI for the intermediate formation of the ate-complex with Cu[I] we achieved an yield 86% of III. There was absolute spectroscopic identity between the products III, IV, V, VI prepared by Schemes 1 and 2.

#### EXPERIMENTAL

<sup>1</sup>H-NMR spectra were recorded on a BRUKER 250 spectrometer in CDCI<sub>3</sub> and TMS as an internal standard. Capillary GC analysis and percentage yield were determined on a CARLO ERBA STRUMENTAZIONE 41300: 0V1, 25m, 150°C, carrier gas H<sub>2</sub>. The standard solution was prepared with octyl ester of benzoic acid and III prepared by Scheme 2.

THF was distilled over Na. The solution of n-BuLi (1.6 M in hexane) and CuI were from ALDRICH. The 3-methoxyphenol and BrCH<sub>2</sub>COOEt were from JANSSEN CHIMICA.

The protection of the hydroxyl group was accomplished with ethyl vinyl ether using trichloroacetic acid as a catalyst.

## Preparation of 2'-hydroxy-6'-methoxyphenylacetic acid ethyl ester

6.37 ml 1.6 M solution of BuLi [0.01 mol] in hexane was injected at room temperature for 30 min into a solution of 2 g [0.01 mol] of II in 15 ml THF. The yellow mixture was stirred for 2 h under N<sub>2</sub>. 1g CuI [0.0055mol] was added carefully and the reaction mixture was stirred 1 h more to insure complete formation of the ate-complex with Cu[I]. The flask was placed in acetone/carbo glass bath at -76°C and 1.1 ml [0.01 mol] BrCH<sub>2</sub>COOEt were injected for 30 min. The cooling bath was removed and the temperature was left to raise for 3.5 hours.

The water and ether were added, the mixture filtered and organic layer washed with 10% Na<sub>2</sub>CO<sub>3</sub> and brine to pH 7. After that the organic solution was dried and evaporated.

The residue was dissolved in ethanol and 20 ml 2M HCI were added. The solution was stirred at room temperature for 15 min. The ethanol was evaporated, ether was added and etheral layer was washed with brine to pH 7, dried and evaporated. The residue was 2.1g yellow oil containing 86% 2'-hydroxy-6'methoxyphenyl acetic acid ethyl ester and was used directly for the further syntheses.

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