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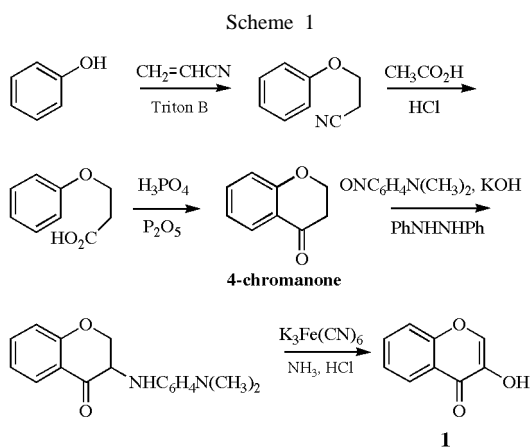
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Received November 14, 2002

A new and efficient 2-step synthesis of 3-hydroxychromone is described. Commercially available chromone is converted to the corresponding epoxide which is rearranged with niobium pentachloride to 3-hydroxychromone in 61% overall yield.

J. Heterocyclic Chem., **40**, 369 (2003).

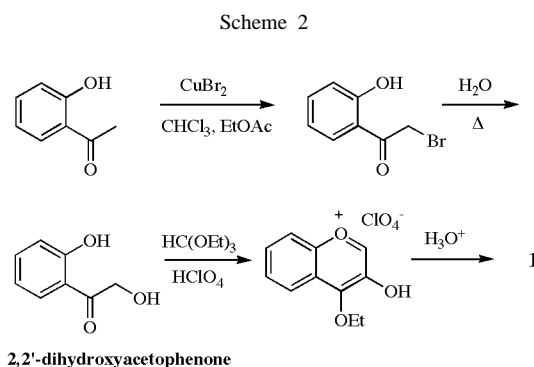
3-Hydroxychromone (**1**) is a chemical substance demanded for several different applications. It has been used as starting material for the synthesis of a number of biologically active natural products [1], as a substrate in studies of excited state proton transfer (ESPT) reactions [2], of fluorescence [3], of acid/base properties [4], and in studies about electronic structure [5]. This compound has the basic structure of a series of natural products, as the flavonoids substituted in positions 2 and 3, that exhibit antibacterial, antioxidant, anticancer, antiallergy, and anti-HIV activity [6].

A number of synthetic routes to 3-hydroxychromone (**1**) have been reported over the years, using different starting materials, with variable yields and number of steps. The most frequently used method was first described by Murata and co-workers [7] (Scheme 1): starting from phenol, compound **1** is obtained in 5 steps with an overall yield of 16%. As one of the intermediates (4-chromanone) is nowadays commercially available, it is now possible to perform only the last two steps of this synthesis to obtain **1**.

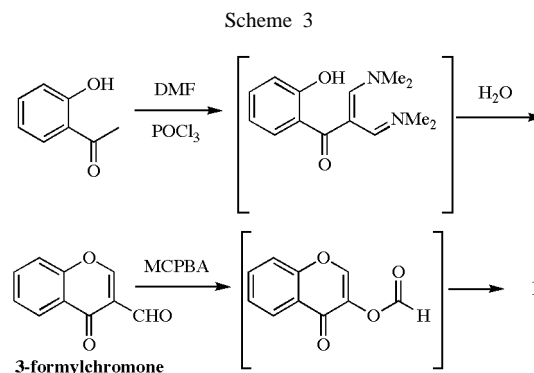


Two syntheses using *o*-hydroxyacetophenone as starting material were described. Becket and co-workers [8] (Scheme 2) used a previously described process [9] to transform the starting material into 2,2'-dihydroxyacetophenone (2 steps) which was converted to **1** through

pyrylium salt formation and hydrolysis. A rather surprisingly high overall yield (86%) was reported for this method.

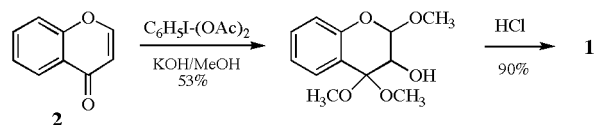


Reddy and co-workers [10] (Scheme 3) first converted *o*-hydroxyacetophenone to 3-formylchromone in 2 steps (61% yield) as previously described by Nohara and co-workers [11], and then performed a Bayer-Villiger oxidation (90% yield) to prepare **1**.



Chromone (**2**) is the starting material for two other syntheses. Moriarty and co-workers [12] (Scheme 4) describe an oxidation of **2** with iodobenzene diacetate followed by acidic hydrolysis, with an overall yield of 48%.

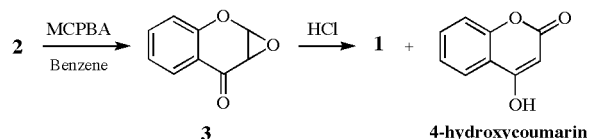
Scheme 4



Srimannarayana and co-workers [13] (Scheme 5) prepared epoxide **3** from **2** with MCPBA; treatment of **3** with HCl gave a mixture containing 3-hydroxychromone (**1**) (24% yield) and 4-hydroxycoumarin as a minor by-product.

As we have recently demonstrated that niobium pentachloride can be used as Lewis acid for epoxides rearrangements [14], we decided to investigate the possibility of preparing 3-hydroxychromone through rearrangement of **3** with this reagent.

Scheme 5

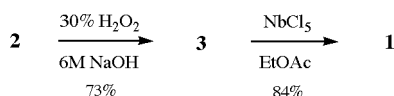


Epoxide **3** was prepared in 73% yield by reaction between chromone (**2**) and 30% H₂O₂ in alkaline medium. This is a useful method for epoxidation of compounds containing a double bond conjugated with a carbonyl group, because it requires only cheap common reagents, and short reaction times (15 minutes in this case), besides giving good yields. Treatment of **3** with NbCl₅ (0.5 equivalent) in ethyl acetate for 1 minute gave 3-hydroxychromone (**1**) in 84% yield as a yellow solid (Scheme 6).

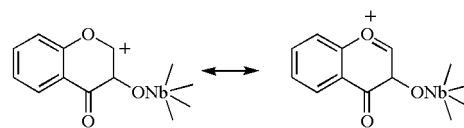
From these results it is clear that the epoxide ring opening, as expected, favors the formation of a carbocation stabilized by the neighboring oxygen atom (Scheme 7).

This is an efficient method for preparing 3-hydroxychromone because only 2 steps are required, a good overall yield (61%) is obtained and both reactions can be performed in very short times at room temperature.

Scheme 6



Scheme 7



EXPERIMENTAL

General.

Chromone (**2**) was purchased from Aldrich Chemical Co. and used without further purification. Melting points are uncorrected. The nmr spectra were measured using a Bruker DRX-400 (400 MHz for ¹H nmr and 100 MHz for ¹³C nmr); deuteriochloroform was used as solvent and tetramethylsilane as internal standard. GC-MS spectra were obtained by EI ionization at 70 eV on a HP-5988-A spectrometer. Infrared (ir) spectra were measured with a Perkin Elmer Spectrum RX I FT-IR System, and the most intense or representative bands are reported (in cm⁻¹). TLC was performed on plates precoated with silica gel 60 F₂₅₄ (0.25 mm thick, Merck).

Chromone epoxide (**3**)

To a solution containing chromone (**2**) (1.0 g, 6.8 mmol) and 30% aqueous hydrogen peroxide (2.0 mL, 21 mmol) in methanol (8 mL) was added drop by drop a 6 M aqueous solution of sodium hydroxide (0.60 mL, 3.3 mmol). During the addition and afterward the temperature of the reaction mixture was maintained at 15-20 °C with a water bath by occasional addition of small portions of ice. After 15 minutes the mixture was diluted with water (8 mL) and extracted with ethyl ether (2 x 10 mL). The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the product was purified by recrystallization using a mixture of methanol and hexane as solvent. Yield of compound **3** as a white solid: 0.805 g (73%), mp 63-64 °C (lit. [15] 65-66 °C); ¹H nmr (400 MHz, deuteriochloroform): δ 7.92 (dd, 1H, J₁ = 8.0 and J₂ = 1.7 Hz); 7.59 (ddd, 1H, J₁ = 8.0; J₂ = 7.1 and J₃ = 1.7 Hz); 7.18 (ddd, 1H, J₁ = 8.0; J₂ = 7.1 and J₃ = 1.0 Hz); 7.08 (dd, 1H, J₁ = 8.4 and J₂ = 1.0 Hz); 5.69 (d, 1H, J = 2.3 Hz); 3.73 (d, 1H, J = 2.3 Hz); ¹³C nmr (100 MHz, deuteriochloroform): δ 188.2 (C=O); 155.4 (C); 136.3 (CH); 127.2 (CH); 123.4 (CH); 119.8 (C); 118.0 (CH); 77.2 (CH); 55.4 (CH); ir (film) ν_{max}: 3054; 2933; 1679; 1607; 1578; 1472; 1383; 1221; 1137; 1005 cm⁻¹; ms *m/z* (rel. intensity) (%): 162 [M⁺] (65); 134 (99); 121 (26); 105 (100); 77 (72); 63 (36); 51 (37); 29 (76).

3-Hydroxychromone (**1**)

To a solution of niobium pentachloride (0.135 g, 0.500 mmol) in anhydrous ethyl acetate (1 mL) maintained at room temperature under nitrogen atmosphere, was added a solution of the epoxide **3** (0.162 g, 1.00 mmol) in anhydrous ethyl acetate (1 mL). After 1 min, the reaction mixture was quenched with a 10% aqueous citric acid solution (2.0 mL). The mixture was diluted with water (5 mL) and ethyl acetate (10 mL), the organic layer was separated and washed with 5% aqueous sodium bicarbonate (3 x 10 mL), saturated brine (2 x 10 mL), and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the product was purified by recrystallization

using a mixture of methanol and hexane as solvent. Yield of compound **3** as a yellow solid: 0.136 g (84%), mp 179-180 °C (lit. [16] 181 °C); ¹H nmr (400 MHz, deuteriochloroform): δ 8.23 (dd, 1H, J₁=8.0 and J₂=1.5 Hz); 8.03 (s, 1H); 7.69 (ddd, 1H, J₁=8.6; J₂=7.1 and J₃=1.5 Hz); 7.50 (d, 1H, J=8.6 Hz); 7.41 (ddd, 1H, J₁=8.0; J₂=7.1 and J₃=1.5 Hz); ¹³C nmr (100 MHz, deuteriochloroform): δ 174.0 (C=O); 156.3 (C); 142.1 (C); 139.9 (CH); 133.6 (CH); 125.5 (CH); 124.8 (CH); 122.5 (C); 118.6 (CH); ir (film) ν_{max}: 3282; 3043; 1637; 1607; 1565; 1472; 1421; 1285; 1154 cm⁻¹; ms m/z (rel. intensity) (%): 162 [M⁺] (71); 134 (29); 120 (10); 105 (100); 77 (48); 51 (39); 50 (44); 29 (48).

Acknowledgments.

The authors thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and the Coordenadoria de Aperfeiçoamento de Pessoal do Ensino Superior (CAPES) for financial support.

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