An Improved and Large Scale Synthesis of the Natural Coumarin Scopoletin

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Summary

Isovanillin was oxidized with magnesium monoperoxyphthalate to 4-methoxyresorcinol (**2**) and the latter was reacted with 3-oxopropionic acid ethylester prepared *in situ* to give scopoletin (**1**). These reactions can be achieved in kg scale in high yields.

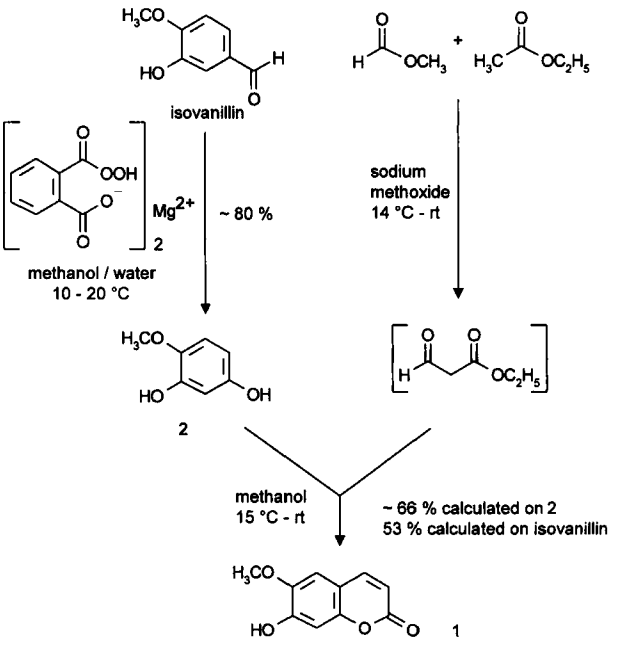
Introduction

7-Hydroxy-6-methoxy-2*H*-1-benzopyran-2-one (scopoletin, **1**), a constituent of many different medicinal plants[1–3], has been intensely investigated as a potentially biologically active (e.g. antimutagenic) compound[3,4], as an intermediate in the synthesis of other coumarins[5,6], and as a reference compound in pharmaceutical analysis[2]. In order to prepare the antiallergic compound 7-[3-[4-[bis(4-fluorophenyl)-hydroxymethyl]-1-piperidinyl]propoxy]-6-methoxy-2*H*-1-benzopyran-2-one (KA-398)[6] on a scale of several kilograms, we required a high yield synthesis of **1**, based on inexpensive and easily available starting materials.

Among others[7], two important synthetic pathways leading to **1** are known. The first one starts from the plant constituent esculin and proceeds in four steps: benzylation, cleavage of the sugar moiety, methylation, and finally debenzylation.[8] The step yields are good with an overall yield of 65 %, but the use of esculin is uneconomical and the availability of large quantities is not guaranteed. The second method is based on the oxidation of 3-hydroxy-4-methoxybenzaldehyde (isovanillin) with peracetic acid yielding 66 % of 4-methoxy-1,3-benzenediol (**2**)[9] followed by a phosphorus acid catalysed Pechmann condensation with 3,3-diethoxypropionic acid ethyl ester[10]. Although distilled **2** is used for the condensation, scopoletin (**1**) precipitates as a tacky solid[10] that is unsuitable for a large scale preparation. A yield of 73 % calculated on **2** is given for the second reaction, corresponding to an overall yield of 48 % of crude **1**. The yield of the purified product is not given[11].

Results and Discussion

In search of an oxidation procedure that is safe and easily performed, we found that the use of magnesium monoperoxyphthalate in methanol/water, described by Heaney[12] for other aromatic aldehydes, gives superior results compared to hydrogen peroxide and to other peracids such as peracetic acid and 3-chloroperoxybenzoic acid. Using this method, we obtain **2** as a red oil in a purity of about 85 % (by ^{1}H-NMR). This crude material is reacted with 3-oxopropionic acid ethyl ester, prepared *in situ* from ethyl acetate and methyl formate in the presence of sodium methoxide by the method given by Steenbergen[13]. This procedure yields 53 % of crude scopoletin (**1**) calculated on the basis of isovanillin as a colourless microcrystalline solid with a purity of about 99 % (according to ^{1}H-NMR)[14]. In contrast to the acidic conditions usually used in the Pechmann reaction, a base is employed as catalyst for the ring closure, since the 3-oxopropionic acid ethyl ester and its acetal, as used by Crosby[10], are not stable in an acidic medium. By running several batches we found that yield and purity vary within a very small range.



The advantages of the method described are (1) a better yield compared with the method given by Crosby[9,10], (2) the use of an oxidizing agent that can be handled safely[12], (3) the relatively low costs of the starting materials, especially compared with esculin, (4) the possibility of using crude **2** for the coumarin ring closure, and (5) the formation of very pure crystalline scopoletin (**1**) without any purification.

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Experimental

Commercially available reagents and solvents were used without further purification. Melting points were determined on a differential scanning calorimeter Seiko DSC 220, using a heating rate of 2 K/min. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AC 200 spectrometer (200 MHz) in [D$_6$]DMSO. The chemical shifts refer to TMS (^{1}H NMR) or to [D$_6$]DMSO (^{13}C NMR, δ = 39.5 ppm), respectively.

4-Methoxy-1,3-benzenediol (**2**)

A solution of 1455 g magnesium monoperoxyphthalate hexahydrate (85 % purity; 2.50 mol) in a mixture of methanol (2.5 L) and water (2.5 L) was added dropwise to a suspension of 609 g 3-hydroxy-4-methoxybenzaldehyde (isovanillin; 4.00 mol) in a mixture of methanol (750 mL) and water (750 mL) keeping the temperature between 10 and 20 °C. The mixture was stirred for 17 h at room temperature and a solution of 143 g sodium disulfite (0.75 mol) in water (250 mL) was added to destroy the excess of the peroxy acid (peroxide test negative). The solution was concentrated to about half the volume (3.5 L) under reduced pressure, the residue was cooled to 4 °C and filtered. The filtrate was extracted with *tert*-butyl methyl ether, the *tert*-butyl methyl ether solution was washed with water, dried with sodium sulfate and evaporated: the remaining dark red oil (525 g) contained about 85 % **2** (yield 80 %).– ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 3.65 (s, 3 H, OCH$_3$), 6.12 (dd, J_1 = 8.6 Hz, J_2 = 2.8 Hz, 1 H, 6-H), 6.27 (d, J = 2.8 Hz, 1 H, 2-H), 6.69 (d, J = 8.6 Hz, 1 H, 5-H), 8.78 (s, 1 H, OH), 8.84 (s, 1 H, OH).– ^{13}C NMR ([D$_6$]DMSO, 50.3 MHz): δ = 56.6 (OCH$_3$), 103.7, 104.8 (C-2, C-6), 114.2 (C-5), 140.7 (C-4), 147.5 (C-3), 151.9 (C-1).

7-Hydroxy-6-methoxy-2H-1-benzopyran-2-one (**1**)

683 g methyl formate (11.4 mol) was added to a suspension of 1150 g sodium methoxide (21.3 mol) in 3.1 L ethyl acetate (31.6 mol) keeping the temperature between 14 and 16 °C by cooling. The mixture was stirred for 18 h at room temperature and a solution of 1595 g crude **2** (purity about 85 %; ~ 9.68 mol from three 4 mol batches) in methanol (8 L) was added keeping the temperature between 15 and 20 °C. The mixture was stirred for a further 18 h at room temperature, was acidified with sulfuric acid (10 L; 1 molar) and diluted with water (8 L). The precipitated product was filtered off, washed with water and dried at 60 °C under reduced pressure to afford 1227 g scopoletin (**1**), mp 204.1 °C (ref.[15] 204–205 °C); yield 66 % calculated on **2**, 53 % calculated on isovanillin. The NMR spectra are in agreement with the data published by Tanaka et al.[16] (^{1}H NMR) and by Sankar et al.[17] (^{13}C NMR).

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