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# An Efficient Synthesis of Isofraxidin

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***Abstract** : An improved procedure for the preparation of **isofraxidin** 1 a well known natural coumarin, through transformation of syringaldehyde is reported. The cyclization of 7 to the coumarinic carboxylic acid 8 is readily performed by cold concentrated sulfuric acid. The overall yield to 1 by this convenient route is near 50%.*

Isofraxidin **1** (or 7-hydroxy-6,8-dimethoxy-2**H**-1-benzopyran-2-one), (scheme I), is a constituent of a great number of plant extracts which exhibit significant pharmacological effects (1). This well-known coumarin, as many other terms of this family, is generally associated to terpenes or sugar compounds (2). The poor availability of **1** is surprising. So far, only two pathways have been described for its preparation : from umbelliferone **2** in a very poor overall yield (less than 1%) (3), and more recently (4) from natural fraxin **3** after hydrolysis by HCl to fraxetin followed by a three steps sequence (overall yield 50%).

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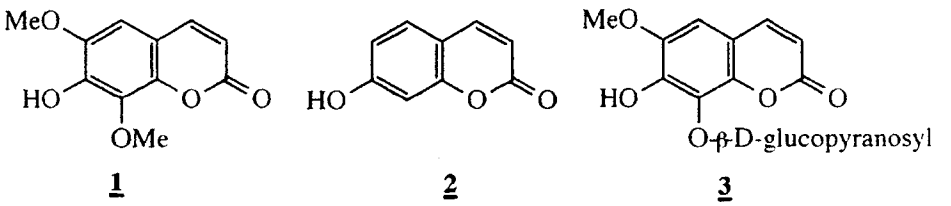
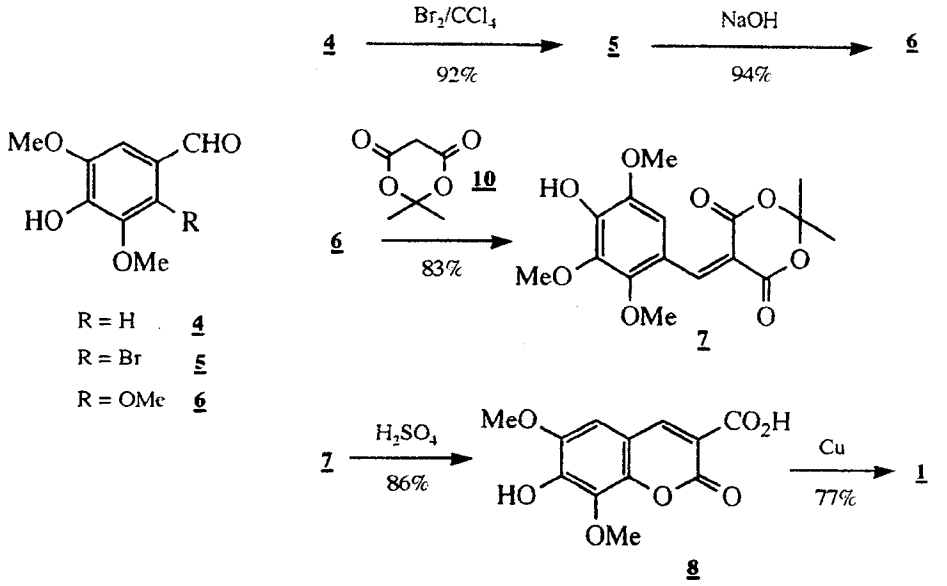
Scheme I




1 2 3

Scheme II




As a part of the synthesis of a family of compounds possessing a coumarin moiety (5), we were in need of a more convenient method to obtain isofraxidin 1. This note report a straigthforward synthesis of it (6).

Based on the possibility to decarboxylate coumarinic acids by copper (7), we devised a sequence represented by scheme II .

The preparation of 2-bromosyringaldehyde **5** (8,9), was carried out by dropwise addition of $Br_2$ dissolved in $CH_2Cl_2$ to a solution of **4** in $CH_2Cl_2$. **5** was recrystallized from ethyl acetate and cyclohexane (1:1 vv) to yield pure **5** (92 %) mp. 189 °C. **5** was refluxed in dry DMF with a ten fold excess of freshly prepared NaOMe in the presence of $CuCl_2$ (0.5 eq.) to induce the homolytic cleavage of the carbon-bromine bond (10). After neutralization and extraction, **6** was obtained in almost quantitative yield. It is worth noting that rigorously anhydrous conditions are required to achieve this latter reaction.

Compound **7** was obtained in heterogeneous medium in the presence of a large excess of ZnO to promote a clean Knoëvenagel type reaction between Meldrum's acid **10** and the aldehyde **6**. Finally the 3-carbethoxycoumarin **8** resulted from a cyclization of the Meldrum's acid derivative in concentrated sulfuric acid medium, a well-known condensing agent for the Von Pechmann reaction, then decarboxylation with powdered copper.

The overall yield from **4** (48% in five steps) compares well with other methods and we find this route straightforward and easier to carry out than any previously published.

## Experimental section

$^1H$ and $^{13}C$ NMR were recorded with a Varian EM90 (MHz) or a Bruker AC400 (MHz) spectrometer for solution in $CDCl_3$. Chemical shifts were reported in ppm ($\delta$) relative to tetramethylsilane as internal standard; coupling constants (J) are given in Hz with the following abbreviations for splitting patterns: s = singlet, ps = pseudo-singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Melting point were taken on a Reichert apparatus and are uncorrected. Flash chromatography was performed on 230-400 mesh Merck Silica gel 60. Elemental analyses of new compounds were performed in the *Service de Microanalyse de l'ICSN* (Gif sur Yvette). High resolution mass spectra were recorded with a Varian MAT311.

**4-hydroxy-2,3,5-trimethoxybenzaldehyde 6**

A 500 mL three-necked round-bottomed flask is fitted with a magnetic stirrer, a condenser with a cirulation of argon, a pressure equalizing funnel and a thermometer. 50 mL of anhydrous methanol is introduced and 4.32 g of sodium (188 mmol), cutted in small pieces, is slowly added. After reaction, methanol is evaporated under reduced pressure. 5 (4.8 g, 18.5 mmol), 23 mL of dimethylformamide and 1 g (7.5 mmol) of $CuCl_2$ are added and heated to reflux 2 hr. This mixture is cooled to room temperature, diluted with 120 mL of water, then acidified with HCl 6N to pH 1. The solution is filtered on a paper filter and extracted with $CH_2Cl_2$. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Crude 6 (4 g) is recrystallized in ethyl acetate/cyclohexane (1:1 vv). 3.67 g of 6 are obtained (94%), mp. 119-120 °C. NMR $^1H$ (90 Mhz) $CDCl_3$, ppm : 3.98 (s, $MeO_{(C2)}$), 4.04 (s, $MeO_{(C3)}$ and $MeO_{(C5)}$), 6.38 (ps, OH), 7.24 (s, $H_{(6)}$), 10.45 (s, $H_{(ald.)}$). Elemental analysis, found C, 56.48; H, 5.51; O, 37.62 %. $C_{10}H_{12}O_5$ requires C, 56.60; H, 5.70; O, 37.70 %. Mass Spectrum (m/z, rel. intensity): 212 (100) $P^+$; 197 (21); 173 (14); 141 (14); 126 (9); 28 (15). HRMS calcd for $C_{10}H_{12}O_5$ 212.06847; Found 212.0680.

**2,2-dimethyl-5-((4-hydroxy-2,3,5-trimethoxyphenyl)-methylene)-1,3-dioxane-4,6-dione 7**

In a 100 mL flask, 2 g of 6 (9.4 mmol), 2 g of Meldrum's acid 10 (14 mmol) (11) and 10 g of zinc oxide (140 mmol) (12) are mixed together. This mixture, turned to orange yellow, was maintained to 80 °C and stirred from time to time for 4 hr. After cooling to room temperature using a water bath, $CH_2Cl_2$ (150 mL) is added. After decantation, the solvent is removed under reduced pressure. Crystallization of crude 7 (3.2 g) from ethanol/water (1:1 vv) afforded pure 7 (2.63 g, 83%) mp. 135-136 °C. NMR $^1H$ (90 Mhz) $CDCl_3$, ppm : 1.84 (s, 6H, 2 $CH_3$), 4.02 (s, $MeO_{(C3)}$ and $MeO_{(C5)}$), 4.00 (s, $MeO_{(C2)}$), 6.65 (ps, OH), 8.32 (s, $H_{(6)}$), 9.03 (s,

$H_{(ethylenic)}$). Elemental analysis, found C, 56.66; H, 5.32; O, 38.57 %. $C_{16}H_{18}O_8$ requires C, 56.80; H, 5.36; O, 37.83 %. Mass Spectrum (m/z, rel. intensity): 338 (21) $P^+$; 281 (12); 280 (34); 250 (11); 249 (100); 207 (17); 195 (18); 193 (15); 43 (10). HRMS calcd for $C_{16}H_{18}O_8$ 338.10016; Found 338.1004.

**7-hydroxy-6,8-dimethoxy-2-oxo-2H-1-benzopyran-3-carboxylic acid 8.**

A mixture of 7 (2g, 5.9 mmol) and 15 mL of concentrated sulfuric acid is stirred at 3-4 °C (ice bath) for 1.5 hr, then slowly poured on crushed ice. The mixture is cooled with an ice bath for 2 hr during which **8** crystallyzes. The crude acid is washed with water and dried under vacuum. This yields 1.35 g (86%) of **8** after crystallization (ethanol/water) mp. 227-228 °C. NMR $^1H$ (400 MHz) DMSO-*d6*, ppm : 3.49 (s, OH), 4.81-4.82 (2s, 6H, 2 $CH_3O$), 8.25 (s,$H_{(5)}$), 9.36 (s, $H_{(4)}$),11.45 (ps, $CO_2H$). Elemental analysis, found : C, 53.95; H, 3.66; O, 41.82 %. $C_{12}H_{10}O_7$ requires C, 54.14; H, 3.79; O, 42.07 %. Mass Spectrum (m/z, rel. intensity): 266 (100) $P^+$; 222 (24); 207 (18); 194 (8); 179 (11); 28 (13). HRMS calcd for $C_{12}H_{10}O_7$ 266.04264; Found 266.0427.

**7-hydroxy-6,8-dimethoxy-2-oxo-2H-1-benzopyran-2-one 1 (isofraxidin).**

A mixture of **8** (1.25 g, 4.7 mmol) and 36 mg of powdered copper (7) placed in a round-bottomed flask (25 mL) fitted with a reflux condenser, is heated under $N_2$ at 300 °C with a metallic bath for 10 min. After cooling 80 mL of water are added. Crude **1** is extracted by $CH_2Cl_2$ (2 * 70 mL). The two phases are separated and the aqueous layer is discarded. The organic layer is dried over anhydrous $MgSO_4$, filtered, and the solvent is removed by evaporation. Crude **1** (885 mg) is purified by crystallization in ethyl acatate/cyclohexane (1:1 vv) mp. 144 °C. NMR $^1H$ (90 MHz) $CDCl_3$, ppm : 4.03 and 4.16 (2s, 6H, 2 $CH_3O$), 6.38 (d, J = 9 Hz, $H_{(3)}$), 6.79 (s, $H_{(5)}$), 7.75 (d, J = 9 Hz, $H_{(4)}$). Elemental analysis, found : C, 58.86; H, 4.54; O, 36.21 %. $C_{11}H_{10}O_5$ requires C, 59.46; H, 4.54; O, 36.00 %. Mass Spectrum (m/z, rel. intensity): 222 (100) $P^+$; 207 (18); 194 (8); 179 (11); 123 (12); 95 (8); 79 (7);

51 (7); 28 (13). HRMS calcd for $C_{11}H_{10}O_5$ 222.05282; Found 222.0524; (M-$CH_3$) calcd 207.02934; Found 207.0297.

## References and notes

(1) a search online in Chem. Abs. database indicated that 1 (mainly as 7-Oβ-D-glucoside) is reported more than 60 times for the period covered by issues 66 to 117. Among these references some are dealing with various ailments.

(2) *see for exemple:* a) F. Bohlmann, C. Zdero and H. Kapteyn, *Lieb.Ann. Chemie,* 1968, **717**, 168.

b) L. Caglioti, H. Naef, D. Arigoni and O. Jeger, Helv. *Chim. Acta,* 1958, **41**, 2278

c) O. Hofer and H. Greger, *Phytochem.*, 1984, **23** (1), 181

d) Späth and Dobrovolny, *Chem. Ber.*, 1938, **71**, 1831

(3) V.K. Ahluwalia, V.N. Gupta, C.L. Rustagi and T.R. Seshadri, *J.Sci. Indus. Research*, 1960, **19**(B), 345

(4) P. Gorecki and A. Mscisz, *Herba Pol.*, 1988, **34**(1-2), 43.

(5) M. Aziz and F. Rouessac, *Tetrahedron,* **44**(1) 101, 1988 - *Tetra. Letters,* 1987, **28** (23), 2579 - *Bull. Soc. Chim. Fr.*, 1988, 555.

(6) Among the great number of different approaches to coumarins that have appeared in the literature (*see* F. M. Dean, "Naturally Occuring Oxygen Compounds"; Butterworths, London 1963, 176), the described methodology employing common intermediates transgresses the preparation of the sole fraxidin; It has been applied in our hands to other coumarins.

(7) This decarboxylation could be also accomplish by means of 25 % aqueous sodium bisulfite, *see* R. Adams and J. Mathieu, *J. Amer. Chem. Soc.*, 1948, **70**, 2120

(8) K. R. Kavanagh and J.M. Pepper, *Can. J. Chem.*, 1954, **32**, 216

(9) T. Iwasaki and K. Takashima, Jpn Kokai Tokkyo Koho JP 03,157,351 [91,157,351]; in our hands, 5 NMR $^1H$ (90 MHz) $CDCl_3$, ppm : 4.02 (s, 6H, 2 MeO), 7.43 (s, $H_{(6)}$), 10.45 (s, $H_{(ald.)}$). Mass Spectrum (m/z, rel. intensity): 262 (99); 261 (69); 260 (100) $P^+$; 259 (39); 110 (11); 95 (13); 77 (11); 53 (11); 28(23).

(10) *see for exemple :* W. Seidenfaden and D. Pawellek, "Methoden der Organische Chemie", Houben-Weyl, Georg Thieme Verlag, Stuttgart 1971,Vol. 10-1, p. 863 ; A. Russel and W.G.Tebbens, Org. Syntheses, 22, 35 (Coll. Vol. III, 1955, 293); M.A. Keegstra, T.H.A. Peters and L. Brandsma, *Tetrahedron,* 1992, **48**(17), 3633; *for a recent book on $S_NAr$ reactions, see :* C. Paradisi, "Arene Substitution *via* Nucleophilic Addition to Electron Deficient Arenes" Comprehensive Organic Synthesis; Pergamon Press; Oxford, 1991; Chapter 1.

(11) purchased from Aldrich Co. or prepared according to D. Davidson and S.A. Bernhard, *J. Amer. Chem. Soc.*, 1948, **70**, 3426
(12) zinc oxide 99.5 %, purchased to Janssen Chimica

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