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Sreenivasan Balasubramanian [a] & Muraleedharan G. Nair [a]

[a] Department of Horticulture and National Food Safety and Toxicology Center, Bioactive Natural Products Laboratory, Michigan State University, East Lansing, Michigan, 48824

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AN EFFICIENT "ONE POT" SYNTHESIS OF ISOFLAVONES

Sreenivasan Balasubramanian and Muraleedharan G. Nair*

Bioactive Natural Products Laboratory, Department of Horticulture and National Food Safety and Toxicology Center, Michigan State University, East Lansing, Michigan 48824.

ABSTRACT: Initial formation of deoxybenzoin **3** from phenyl acetic acid **1** and phenol **2** in the presence of $BF_3.Et_2O$ followed by its treatment at room temperature with N, N'-dimethyl (chloromethylene) ammonium chloride, generated by reacting PCl_5 with DMF provides a mild and efficient route for a "one pot" synthesis of Isoflavones in high yields.

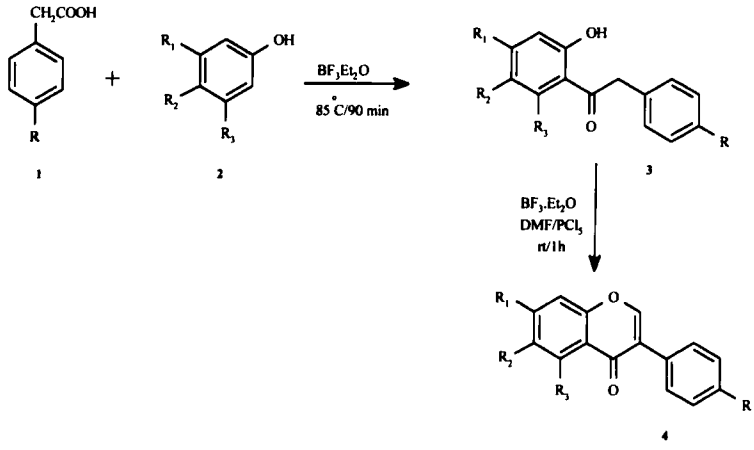
Isoflavones are a class of compounds mainly occurring in species of the Leguminosae family. These compounds have received much attention recently due to their interesting biological activities[1]. We have shown that[2] the isoflavone, formononetin, isolated from the roots of clover plants is very effective in stimulating the growth of vesicular arbuscular mycorrihzal fungi (AM) and enhances the growth of many plant species that are host to AM. Most of the isoflavones have been isolated from natural sources and their simple structural features lead to the development of many synthetic methods. However, most of

* To whom correspondence should be addressed.

the available methods utilize special and expensive reagents in large excess to achieve the reported yield. Long reaction times, vigorous conditions, very low yield of the desired products and complex reaction products which require laborious purification of the final product are some of the major drawbacks of these methods. These published methods are based on two strategies, (1) the deoxybenzoin route[3] wherein the deoxybenzoin is treated with a one carbon activated system like N,N'-dimethylformamide dimethyl acetal followed by ring closure leading to the formation of isoflavone and (2) the chalcone route[4] which involves the conversion of a chalcone to isoflavone by oxidative rearrangement using reagents like thallium nitrate. Other methods like the hypervalent iodine oxidation of flavanone[5a], epoxidation of the chacone followed by rearrangement and debenzylative cyclization[5b], palladium catalysed cross coupling reaction of 3-bromochromone with arylboronic acid[5c] and by the condensation of enamine with salicylaldehyde[5d] are also used for the synthesis of isoflavones. We have earlier reported[6] a rapid synthesis of isoflavones using microwave energy for the one carbon addition and cyclization. Formononetin is currently marketed as an AM stimulating agent under the trade mark "Mycoform™" by VamTech, L.L.C. Therefore, the need for large quantities of formononetin has prompted us to develop a mild and cost effective method that can be scaled up to ton quantities. In this communication we report a method which can be carried out in "one pot" under mild conditions. (Scheme 1).

The method involved the preparation of deoxybenzoins from respective substituted phenols and phenyl acetic acids by Friedel Crafts Acylation using boron trifluoride etherate which served as the Lewis acid for the acylation and as solvent for the reaction. The acylation was carried out at 85°C. In most cases the reaction was completed within 90 min. In the case of "one pot' method, the deoxybenzoin obtained was directly treated with the reagent, N, N'-dimethyl(chloromethylene) ammonium chloride[7]. This reagent was generated separately by treating phosphorous pentachloride with N,N'-dimethylformamide.

Scheme 1



The reaction proceeded smoothly at room temperature and the respective isoflavones were obtained by pouring the reaction mixture either into boiling dilute HCl or methanolic HCl. The yields and melting points of various isoflavones prepared are summarised in the Table 1.

The synthesis of these isoflavones was conducted as a two step process also, where the intermediate deoxybenzoins were isolated and purified followed by their conversion to respective isoflavones. In the "one pot" method a minimum of 5 equivalents of $BF_3.Et_2O$ and 1-1.5 equivalents of PCl_5 were required for the completion of the reaction. Similarly, in the two step process, a minimum of 3 equivalents of $BF_3.Et_2O$ was used to convert the deoxybenzoin to its corresponding isoflavone and the reaction required the presence of $BF_3.Et_2O$.

When the reaction mixture was poured into either boiling dilute HCl or methanolic HCl, initially a bright yellow product precipitated which then slowly converted to isoflavones. The work-up procedure differed slightly in the

Table 1

Entry	R	R_1	R_2	R_3	Isoflavone (4) Yield (%)	M.p [°C][c] Observed
a	H	OH	H	H	80	210 - 213
b	H	OCH_3	H	H	85	157 - 159
c	OH	OH	H	H	92	320 (dec.)
d	OCH_3	OH	H	H	90	257 - 258
e	OH	OCH_3	H	H	82	218 - 220
f	OCH_3	OCH_3	H	H	75	162 - 164
g	OH	H	OH	H	65	160 - 162
h	OH	H	H	OH	92[a]	168 - 170
i	OCH_3	H	H	OH	94[a]	140 - 142
j	OH	OH	H	OH	90[a,b]	295 (dec.)
k	OCH_3	OH	H	OH	92[a,b]	211 - 212

[a] Deoxybenzoins were isolated and then converted to isoflavones.

[b] Deoxybenzoins were prepared according to the method mentioned in Ref.6.

[c] For reference M.p. and literature see experimental section.

preparation of some of the isoflavones (Table 1) where the reaction mixture was poured into methanolic HCl followed by heating to 70°C for 30 min.

The reaction involving the formation of isoflavone from deoxybenzoin always proceeded smoothly. The substitution pattern as well as the presence of unprotected hydroxyl groups on the aromatic rings did not influence the reaction time and the product yield. However, the formation of deoxybenzoin by $BF_3.Et_2O$ was dependent on the substitution pattern and the nature of the substituents on aromatic rings. Therefore, deoxybenzoins **3j** and **3k** were prepared by a reported procedure[6] and then converted to their respective isoflavones **4j** and **4k** in very high yields.

In summary, the method described in this paper is a mild and efficient process for a "one pot" synthesis of isoflavones. It is cost effective and a large scale production has already been achieved. This confirms the simplicity of this method. Preliminary studies on the nature of the yellow intermediate obtained during the work-up procedure indicated that it is not a formyl derivative of **3** or an hydroxyl derivative of **4**. Work is in progress to characterize this intermediate. The synthesis of many other natural products utilizing this methodology where the addition of single carbon is required will be reported soon.

Experimental

General Information

The melting points were determined on a Bristoline micro melting point

apparatus and were uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian VXR 300 MHz spectrometer and the chemical shifts are expressed in ppm: s, singlet; d, doublet; m, multiplet. The products were purified either by recrystallization or by column chromatography. The starting materials used were purchased from Aldrich chemical company and were used without any further purification. Two methods were used for the synthesis of isoflavones: **Method A** is a "one pot" synthesis and **Method B** is a two step process where the intermediate deoxybenzoin was isolated and purified.

General Procedure for Method A

A mixture of **1** (3 mmol), **2** (3 mmol) and BF_3. Et_2O (1.94 mL, 15.3 mmol) was heated (85°C) for 90 min with stirring. The mixture was then cooled to 10°C and DMF (4.6 mL) was added dropwise. In another flask, DMF (8 mL) was cooled to 10°C and PCl_5 (0.939 g, 4.5 mmol) was added in small portions. The mixture was then allowed to stand at 55°C for 20 min. The pale pink colored solution containing N, N'-dimethyl(chloromethylene)ammonium chloride was then added to the above reaction mixture slowly. During the addition, the temperature of the reaction mixture was maintained below 27°C. The mixture was then stirred at room temperature for 1h. The workup was carried out by two ways. (1) By pouring the reaction mixture slowly into boiling HCl (0.1 N) and filtering the precipitated product (2) by pouring the reaction mixture into methanolic HCl (0.1 N) followed by heating at 70 °C for 20 min and extracting the product after removing the methanol and most of DMF. Isoflavones which precipitated from dilute HCl were filtered off, washed with water

and air dried. The products were further purified by recrystallization from aqueous methanol or by column chromatography on silica (15 g, Silica gel 60, 35-70 μm, E.Merck), using EtOAc/Hex. Isoflavones which separated out as a sticky mass were extracted with EtOAc. The organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was removed under vacuum using a rotary evaporator and the crude product was purified by recrystallization or by column chromatography.

General procedure for Method B:

A mixture of **1** (3 mmol), **2** (3 mmol) and BF_3. Et_2O (1.94 mL, 15.3 mmol) was heated (85°C) for 90 min with stirring. The mixture was then poured into NaOAc solution (100 mL, 10 %) and allowed to stand for 4 h. The product was filtered, washed with water and air dried. The deoxybenzoins (**3a -3k**) were purified by recrystallization from aqueous methanol or by column chromatography on silica using EtOAc/Hex. The purified materials were then used for the synthesis of isoflavones.

A mixture of deoxybenzoin (3 mmol) and BF_3. Et_2O (1.2 mL, 9 mmol) was cooled to 10°C and DMF (4.6 mL) was added dropwise. The cyclization procedure and workup are similar to Method A.

7-Hydroxy-3-phenyl-4H-1-benzopyran-4-one (7-hydroxyisoflavone) 4a

Method A: Methanolic HCl was used for the workup and the product was purified by column chromatography to yield 0.573 g (80 %) of product as white solid. M.p. 210 - 212°C (lit.[4a] 211-213°C), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.35 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.58 (m, 2H), 7.47 (m, 3H), 6.92 (dd,

J = 9 Hz & 2.1 Hz, 1H), 6.86 (d, J= 2.4 Hz, 1H).

Method B: [1-(2,4-dihydroxyphenyl)-2-(phenyl)ethanone] 2,4-dihydroxy deoxybenzoin 3a. The product was purified by recrystallization from aqueous methanol. 0.583 g (85 %). Pale yellow solid, M.p. 110-113 °C (lit[8]. 110-113 °C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.0 (d, J = 9.0 Hz, 1H), 6.45 (m, 5H), 5.53 (dd, J = 9.3 Hz & 2.4 Hz, 1H), 5.44 (d, J = 2.4 Hz, 1H), 3.77 (s, 2H).

4a was obtained as a white solid, 0.646 g (82 %). M.p. 211 - 212°C.

7-Methoxy-3-phenyl-4H-1-benzopyran-4-one (7-methoxyisoflavone) 4b

Method A: The starting material resorcinol monomethyl ether was prepared according to the published procedure[9]. Methanolic HCl was used for the workup and the product was purified by column chromatography to yield 0.642 g (85 %). M.p. 157 - 159 °C (lit.[10] 158-160 °C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.01 (d, J = 9 Hz, 1H), 7.56 (d, J = 6.6 Hz, 2H), 7.41 (m, 3H), 7.12 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H).

Method B: [1-(2-hydroxy-4-methoxyphenyl)-2-(phenyl)ethanone] 2-hydroxy-4-methoxy deoxybenzoin 3b. The product was purified by column chromatography to yield 0.689 g (95 %). M.p. 86 - 88°C (lit.[11] 88°C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 12.73 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.26 - 7.34 (m, 4H), 6.44 (m, 2H), 4.22 (s, 2H), 3.83 (s, 3H).

4b was obtained as a white solid, 0.680 g (90 %). M.p. 157 - 158 °C.

7-Hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (Daidzin) 4c.

Method A: This product was obtained by the dilute HCl workup of the

reaction product. The product was then purified by recrystallization to yield 0.701 g (92 %). M.p. 320°C, dec. (lit.[12] 320-321°C, dec.) ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.51 (s, 1H), 8.28 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.36 (d, J = 8.7 Hz, 2H), 6.92 (dd, J = 6.6 Hz and 2.1 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H).

Method B: **[1-(2,4-Dihydroxyphenyl)-2-(4-hydroxyphenyl) ethanone] 2,4,4'-trihydroxy deoxybenzoin 3c**. The product was purified by recrystallization to yield 0.680 g (93 %). M.p. 190 - 192°C (lit.[13] 192°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.59 (s, 1H), 10.67 (s, 1H), 9.28 (s, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.06 (d, J = 9.3 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 6.36 (dd, J = 8.7 Hz and 2.4 Hz, 1H), 6.23 (d, J = 2.7 Hz, 1H), 4.11 (s, 2H).

4c was obtained as white solid, 0.685 g (90 %). M.p. 318 - 320°C, dec.

7-Hydroxy-3-(4-methoxyphenyl)-4H-1-benzopyran-4-one (Formononetin) 4d

Method A: The product was obtained by the dilute HCl workup of the reaction product. The crude product was purified by column chromatography to yield 0.721 g (90 %). M.p. 257-258°C (lit.[12] 257-258°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.32 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.91 (dd, J = 6.0 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 3.77 (s, 1H).

Method B: **[1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenyl) ethanone] 2,4-dihydroxy-4'-methoxy deoxybenzoin 3d**. The product was purified by recrystallization to yield a white crystalline solid, 0.688 g (89 %), M.p. 158 - 160°C

(lit.[12] 159°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.63 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.36 (dd, J = 9.0 Hz, 1H), 6.23 (d, J = 2.1 Hz, 1H), 4.18 (s, 2H), 3.7 (s, 3H).

4d was obtained as a white solid after recrystallization 0.680 g (85 %). M.p. 257-258°C.

7-Methoxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (7-methoxy-4'-hydroxyisoflavone) 4e.

Method A. Methanolic HCl method was used for the workup and the product was purified by column chromatography to yield 0.658 g (82 %). M.p. 218-220°C (lit.[14] 218-220°C).

^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.33 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 2.4 Hz, 1H), 7.05 (d,d J = 8.7 Hz & 2.4 Hz, 1H), 6.79 (d, J = 9 Hz, 2H), 3.87 (s, 3H).

Method B. [1-(2-Hydroxy-4-methoxyphenyl)-2-(4-hydroxyphenyl) ethanone] 2,4'-dihydroxy-4-methoxy deoxybenzoin 3e. The product was purified by column chromatography to yield a white crystalline solid, 0.680 g (88 %). M.p. 215 - 216°C (Lit.[15]) ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.59 (s, 1H), 9.26 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 6.49 (m, 2H), 4.16 (s, 2H), 3.79 (s, 3H).

4e was obtained as a white solid, 0.666 g (83 %). M.p. 218 - 220°C.

7-Methoxy-3-(4-methoxyphenyl)-4H-1-benzopyran-4-one (7,4'-dimethoxy isoflavone) 4f

Method A: Methanolic HCl method was used for the workup and the

product was purified by column chromatography to yield 0.633 g (75 %). M.p. 162-164°C (lit.[16]162-164°C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 9 Hz, 1H), 7.89 (s, 1H), 7.48 (d, J = 9 Hz, 2H), 6.95 (m, 3 H), 6.83 (d, J = 2.4 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H).

Method B: [1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl) ethanone] 2-hydroxy-4,4'-dimethoxy deoxybenzoin 3f. The product was purified by column chromatography to yield a pale yellow crystalline solid, 0.636 g (78 %). M.p. 101 - 103°C (lit.[17] 102.5-104°C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 12.72 (s, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.16 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.42 (m, 2H), 4.13 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H).

4f was obtained as a white solid, 0.676 g (80 %). M.p. 162 - 164°C.

6-Hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (6,4'-dihydroxy isoflavone) 4g

Method A. Methanolic HCl method was used for the workup and the product was purified by column chromatography to yield 0.495 g (65 %), M.p. 160 - 162 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.50 (s, 1H), 8.37 (s, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.23 (dd, J = 9.0 Hz & 3.0 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 6.53 (s, 1H).

Method B: [1-(2,5-Dihydroxyphenyl)-2-(4-hydroxyphenyl) ethanone] (2,5,4'-trihydroxy deoxybenzoin) 3g. The product was purified by recrystallization to yield 0.584 g (80 %). M.p. 138 - 141°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.43 (s, 1H), 9.34 (s, 1H), 7.11 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 9.3 Hz, 2H), 6.72 (m, 2H), 6.54 (s, 1H), 3.73 (s, 2H).

4g was obtained as a white solid, 0.533 g (70 %). M.p. 160 - 162 °C.

5-Hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (5,4'-dihydroxy isoflavone) 4h

Method A: The product was obtained as a byproduct in the synthesis of Diadzen **4c**. 0.038 g (5 %). M.p. 168 -170°C (lit.[4a] 169-171°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.77 (s, 1H), 9.63 (s, 1H), 8.49 (s, 1H), 7.65 (t, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.83 (m, 2H).

Method B: [1-(2,6-Dihydroxyphenyl)-2-(4-hydroxyphenyl) ethanone] 2,6,4'-trihydroxy deoxybenzoin 3h. The product was obtained as a byproduct in the synthesis of **3c**. 0.043 g (6 %). M.p. 186 - 188°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.49 (s, 2H), 9.20 (s, 1H), 7.19 (t, J = 8.4 Hz, 1H), 7.0 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.35 (d, J = 8.1 Hz, 2H).

4h was prepared from **3h** and purified by recrystallization. (92 %) M.p 169 -170°C.

5-Hydroxy-3-(4-methoxyphenyl)-4H-1-benzopyran-4-one (5-hydroxy-4'-methoxy isoflavone) 4i

Method A: The product was obtained as a byproduct in the synthesis of Formononetin **4d** 0.04 g (5 %). M.p. 140 - 142°C (lit.[4a] 141-143°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.66 (s, 1H), 7.94 (s, 1H), 7.52 (t, J = 8.7 Hz, 1H), 7.45 (d, J = 5.7 Hz, 2H), 6.90 (m, 4H), 3.83 (s, 3H).

Method B: [1-(2,6-Dihydroxyphenyl)-2-(4-methoxyphenyl) ethanone] 2,6-dihydroxy-4'-methoxy deoxybenzoin 3i. The product was obtained as a byproduct in the synthesis of **3d**. 0.054 g (7%). M.p. 123 - 125°C. ^{1}H-NMR (300

MHz, DMSO-d_6) δ 11.50 (s, 1H), 7.20 (t, J = 9.0 Hz, 1H), 7.12 (d, 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.36 (d, J = 8.1 Hz, 2H), 4.28 (s, 2H), 3.71 (s, 3H).

4i was prepared from **3i** and purified by column chromatography (94 %). M.p. 141-143°C.

5,7-Dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (Genistein) 4j

The product could not be prepared by the "one pot" method due to the failure of the first step reaction to form deoxybenzoin.

Method B: [1-(2,4,6-Trihydroxyphenyl)-2-(4-hydroxyphenyl) ethanone] 2,4,4'6-tetrahydroxy deoxybenzoin 3j. The product was prepared according to the procedure mentioned in Ref. 6. (45 %). M.p. 258 - 259°C (lit.[18] 259°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.24 9s, 2H), 10.39 (s, 1H), 9.20 (s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.7 Hz, 2H), 5.79 (s, 2H), 4.19 (s, 2H).

4j was obtained by following the dilute HCl workup. The product was purified by recrystallization to yield 0.729 g (90 %). M.p. 295°C dec. (lit.[12] 295-296°C, dec.). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.94 (s, 1H), 10.88 (s, 1H), 9.59 (s, 1H), 8.30 (s, 1H), 7.35 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.36 (d, J = 2.1 Hz, 1H), 6.21 (d, J = 2.4 Hz, 1H).

5,7-Dihydroxy-3-(4-methoxyphenyl)-4H-1-benzopyran-4-one (Biochanin A) 4k

The product could not be prepared by the "one pot" method due to the failure of the first step reaction to form deoxybenzoin.

Method B: [1-(2,4,6-Trihydroxyphenyl)-2-(4-methoxyphenyl) ethanone] 2,4,6-trihydroxy-4'-methoxy deoxybenzoin 3k. The product was

prepared according to the procedure mentioned in Ref. 25. (47 %). M.p. 192 - 193°C (lit.[18] 192-193°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.21 (s, 1H), 10.36 (s, 1H), 8.91 (s, 1H), 7.12 (d, J = 8.1 Hz, 2H), 6.83 (d, J = 7.5 Hz, 2H), 5.79 (s, 2H), 4.24 (s, 2H), 3.72 (s, 3H).

4k was obtained by following the dilute HCl workup procedure. The product was purified by recrystallization to yield 0.783 g (92 %). M.p. 211 - 212 °C (lit.[12] 212 °C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.92 (s, 1H), 10.90 (s, 1H), 8.36 (s, 1H), 7.48 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.38 (d, J = 2.1 Hz, 1H), 6.22 (d, J = 2.1 Hz, 1H), 3.77 (s, 3H).

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