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A mild and efficient protocol to synthesize chromones, isoflavones, and homoisoflavones using the complex 2,4,6-trichloro-1,3,5-triazine/dimethylformamide

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Abstract: A mild and efficient one-flask method has been developed for the synthesis of chromones, isoflavones, and homoisoflavones from 2-hydroxyacetophenones, deoxybenzoins, and dihydrochalcones, respectively, via one-carbon extension using the complex 2,4,6-trichloro-1,3,5-triazine/dimethylformamide. Deoxybenzoins and dihydrochalcones were prepared in situ by the reaction of readily available substituted phenols with phenylacetic acids and 3-phenylpropanoic acids, respectively. This method allows the synthesis of a wide range of compounds with multiple phenolic hydroxyls and other substituents. The methodology has been applied to the synthesis of three naturally occurring isoflavones such as formononetin (**9c**), daidzein (**9d**), and retusin (**9h**).

Key words: chromone, isoflavone, homoisoflavone, $BF_3{\cdot}Et_2O$, cyanuric chloride, dimethylformamide.

Résumé : On a mis au point une méthode monotope douce et efficace de synthèse de chromones, d'isoflavones et d'homoisoflavones à partir de 2-hydroxyacétophénones, de désoxybenzoïnes et de dihydrochalcones respectivement par allongement de la chaîne carbonée d'un atome en utilisant le complexe 2,4,6-trichloro-1,3,5-triazine/diméthylformamide. Les désoxybenzoïnes et les dihydrochalcones ont été préparées in situ par réaction de phénols substitués faciles à obtenir avec des acides phénylacétiques et des acides 3-phénylpropanoïques respectivement. Cette méthode permet de synthétiser une vaste gamme de composés portant plusieurs groupements hydroxyles phénoliques et d'autres substituants. La méthode a été appliquée à la synthèse de trois isoflavones naturelles, à savoir la formononétine (**9c**), la daïdzéine (**9d**) et la rétusine (**9h**). [Traduit par la Rédaction]

Mots-clés : chromone, isoflavone, homoisoflavone, $BF_3{\cdot}Et_2O$, chlorure cyanurique, diméthylformamide.

Introduction

The ubiquitous chromones (4*H*-chromen-4-ones) have attracted more attention in both industrial and academic fields for decades.[1] This interest arises from the fact that a variety of natural and synthetic compounds that contain the chromone substructure exhibit several biological activities such as anticancer,[2] antiinflammatory,[3] antioxidant,[4] antimutagenic,[5] antihypertensive,[6] and antiviral activities.[7] They also act as tyrosine and protein kinase inhibitors.[8] Because of their broad range of significant biological activities, synthetic approaches to chromones have been extensively investigated. Isoflavones[9] (3-phenyl-4*H*-chromen-4-ones) and homoisoflavones[10] (3-benzyl-4*H*-chromen-4-ones) are naturally occurring compounds and structurally related to flavanoids and display a wide spectrum of biological activities. Isoflavones are mostly synthesized through oxidative rearrangement of the corresponding chalcone[11] or from deoxybenzoin by one-carbon extension using dimethylformamide (DMF) – dimethyl acetal[12] or DMF/$MeSO_2Cl$[13] or DMF/PCl_5.[14] Few methods have been reported for synthesis of homoisoflavones and these were based on (*i*) the condensation of 4-chromonones with arylaldehydes and then followed by isomerisation of the double bond using Pd/C at 250 °C[15] and (*ii*) one-carbon extension of dihydrochalcone by using HCO_2Et/Na[16] or $HC(OEt)_3$/$HClO_4$[17] or DMF/$MeSO_2Cl$[18] or DMF/PCl_5.[19] However, most of the methods reported for the synthesis of chromones, isoflavones, and homoisoflavanoids suffer from harsh reaction conditions, poor substituent tolerance, long reaction times, and low to moderate yields. Therefore, developing a milder and more general procedure for chromones, isoflavones, and homoisoflavanoids is still highly desirable.

Over the past few years, there has been considerable interest in using 2,4,6-trichloro-1,3,5-triazine (TCT) in organic synthesis.[20] TCT is a stable, nonvolatile, inexpensive, commercially available, and easy-to-handle reagent. Recently, the TCT/DMF complex has been used for several organic transformations such as the conversion of primary alcohols to the corresponding formate esters,[21] Beckmann rearrangement of oximes,[22] conversion of alcohols to alkyl chlorides,[23] and preparation of pyrazoles[24] and carboximides.[25]

On this basis and our interest in the chemistry of flavanoids[19,26] and increasing demand for a short and efficient method, herein we reported a new and general method for the synthesis of chromones, isoflavones, and homoisoflavones using the TCT/DMF complex (Schemes 1 and 2). The methodology has been applied to the synthesis of naturally occurring isoflavones such as formononetin (**9c**),[27] daidzein (**9d**),[28] and retusin (**9 h**).[29]

Results and discussion

Initial efforts were focused on the synthesis of chromones (**2**). In a typical experiment, a mixture of substituted 2-hydroxyacetophenone (**1a**) (1 mL, 3 mmol) and 46% $BF_3{\cdot}Et_2O$ (1.98 mL, 7.5 mmol), was cooled to 10 °C and DMF (4.6 mL) was added dropwise to the reaction mixture. Then, the TCT/DMF complex, prepared in situ from TCT (0.82 g, 4.5 mmol) and DMF (1 mL), was added to the reaction mixture and heated to 60 °C in an oil bath for another 40 min. The reaction mixture was then poured into 3 N HCl, extracted with EtOAc, dried, and concentrated to give crude chromone. The pure compound (**2a**) was then harvested with column chromatography.

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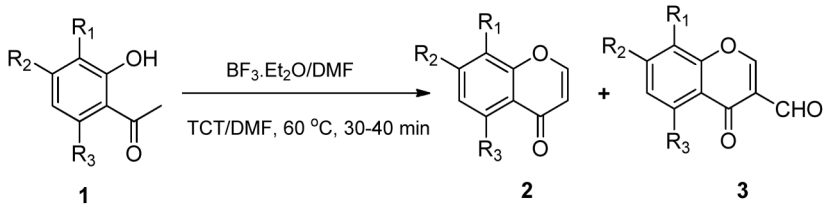
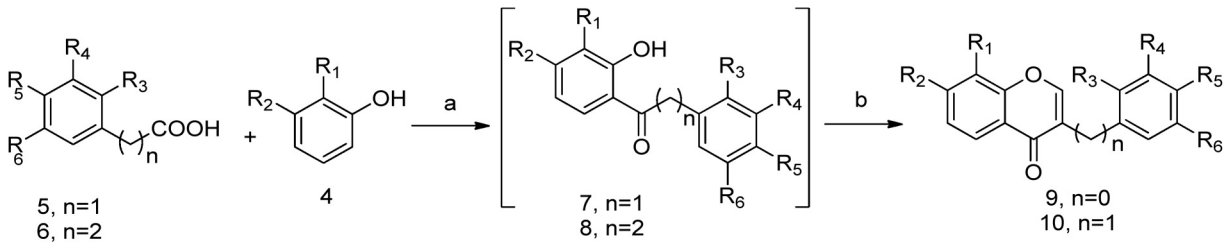
Scheme 1. Synthesis of chromones (**2a–2d**).



Scheme 2. Synthesis of isoflavones (**9a–9h**) and homoisoflavones (**10a–10f**).



Reagents and conditions: (a) $BF_3.Et_2O$, 90 °C. 90 min. (b) DMF, 10 °C; TCT/DMF, 60 °C, 30-40 min.

To further examine the scope of this reaction, various 2-hydroxyacetophenones (**1b–1d**) were also tested. In all cases, the reaction was completed in 40 min and the corresponding products were obtained in 65%–78% yield (Table 1). It was noted that when the unsubstituted 2-hydroxyacetophenone (**1a**) (Table 1) and resacetophenone (**1b**) (Table 1) were taken as substrates, the corresponding 3-formylchromones (**3**) were obtained as byproducts. It is noteworthy that the protection of hydroxyl groups on the aromatic ring is not necessary in this reaction.

After successfully synthesizing chromones (**2a–2d**) in good yields, we turned our attention towards the synthesis of isoflavones (**9**) and homoisoflavones (**10**). The synthesis involved the preparation of deoxybenzoins (**7a–7h**) and dihydrochalcones (**8a–8f**) via Friedel–Crafts acylation of substituted phenols with phenylacetic acids and phenylpropanoic acids, respectively, using $BF_3{\cdot}Et_2O$ in which $BF_3{\cdot}Et_2O$ served as the Lewis acid for the acylation and solvent for the reaction. The acylation was carried out at 90 °C. In most of the cases, the reaction was completed within 90 min. In the case of the one-flask method, the deoxybenzoins (**7a–7h**) and dihydrochalcones (**8a–8f**) obtained were directly treated with the TCT/DMF complex generated in situ from TCT and DMF for one-carbon extension to obtain isoflavones (**9a–9h**) and homoisoflavones (**10a–10f**), respectively, in good yields (Tables 2 and 3). In all cases, the reaction was completed in 30–40 min and the products were characterized by their spectral data (IR, NMR, and mass spectrometry). The synthesis of isoflavones and homoisoflavones was also conducted in a two-step process where the intermediate deoxybenzoins and dihydrochalcones were isolated and purified followed by their conversion into the corresponding isoflavones and homoisoflavones, respectively. The methodology has been applied to the synthesis of naturally occurring isoflavones formononetin (**9c**), daidzein (**9d**), and retusin (**9h**). Deoxybenzoins **7c** and **7d** were synthesized by the reaction of resorcinol with 4-methoxyphenylacetic acid and 4-hydroxyphenyl acetic acid, respectively, in the presence of $BF_3{\cdot}Et_2O$, which were (without purification) converted further into **9c** (90% yield) and **9d** (88% yield) using the TCT/DMF complex. Reaction of pyrogallol and 4-methoxyphenylacetic acid with $BF_3{\cdot}Et_2O$ gave deoxybenzoin (**7h**), which was converted further into **9h** (89% yield). The spectral data of synthetic **9c**, **9d**, and **9h** were found to be identical to those of the corresponding natural products.

Table 1. Synthesis of chromones (**2a–2d**).

S. No.	Entry	R_1	R_2	R_3	**2** yield (%)[a]	**3** yield (%)[a]
1	a	H	H	H	65	15
2	b	H	OH	H	70	13
3	c	OH	OH	H	75	
4	d	H	OH	OH	78	

[a]Unoptimized condition.

Table 2. Synthesis of isoflavones (**9a–9h**).

S. No.	Entry	R_1	R_2	R_3	R_4	R_5	R_6	**9** yield (%)[a]
1	a	H	OH	H	H	H	H	87
2	b	H	OH	H	OCH_3	H	H	89
3	c	H	OH	H	H	OCH_3	H	90
4	d	H	OH	H	H	OH	H	88
5	e	H	OH	OCH_3	H	OCH_3	H	85
6	f	OH	OH	H	H	H	H	78, 88[b]
7	g	OH	OH	H	OCH_3	H	H	75, 85[b]
8	h	OH	OH	H	H	OCH_3	H	75, 89[b]

[a]Unoptimized condition.
[b]Deoxybenzoins were isolated and converted into isoflavones (method B).

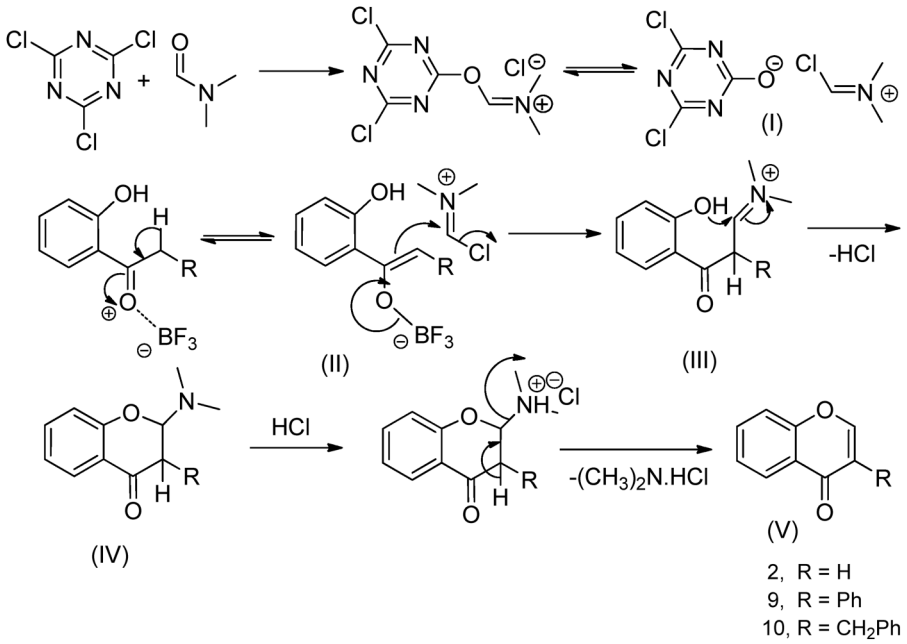
Table 3. Synthesis of homoisoflavones (**10a–10f**).

S. No.	Entry	R_1	R_2	R_3	R_4	R_5	R_6	**10** yield (%)[a]
1	a	H	OH	H	H	H	H	82
2	b	H	OH	H	H	OCH_3	H	85
3	c	H	OH	H	H	OH	H	88
4	d	H	OH	OCH_3	H	H	OCH_3	85
5	e	OH	OH	H	H	OCH_3	H	75, 86[b]
6	f	OH	OH	OCH_3	H	H	OCH_3	78, 85[b]

[a]Unoptimized condition.
[b]Dihydrochalcones were isolated and converted into homoisoflavones (method B).

To explain the formation of chromones (**2**), isoflavones (**9**), and homoisoflavones (**10**) using TCT/DMF, a suggested mechanism is shown in Fig. 1. This mechanism involves the formation of a Vilsmeier–Haack type complex (I) by using cyanuric chloride and DMF. This complex adds to the acetophenone·BF_3 complex (II) to form III, with subsequent nucleophilic attack of the hydroxyl group of 2-hydroxyacetophenone to form IV, which is deaminated to form the final product V.

Fig. 1. Plausible mechanism for the formation of **2, 9**, and **10**.



Conclusion

We have developed a mild, efficient, and economical one-flask method for the synthesis of chromones, isoflavones, and homoisoflavones using the TCT/DMF complex. The methodology has been applied to the synthesis of three naturally occurring isoflavones. Operational simplicity, mild reaction conditions, short reaction times, and good yields are the notable advantages of this method. Chromones, isoflavones, and homoisoflavones are biologically and pharmaceutically active molecules; therefore, the present method will be of wide application in organic chemistry and medicinal chemistry.

Experimental

General remarks

All synthesized compound melting points were recorded on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer BX1 FTIR spectrophotometer and ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer using TMS as the internal standard and the values for chemical shifts (δ) being given in parts per million and coupling constants (*J*) in hertz. Mass spectra were recorded on an Agilent 1100 LC/MSD. Acme silica gel G and silica gel (100–200 mesh) were used for analytical thin-layer chromatography and column chromatography, respectively.

General experimental procedure for chromones (2a–2d)

2,4,6-Trichloro-1,3,5-triazine (TCT) (0.82 g, 4.5 mmol) was added to DMF (1 mL) and stirred at room temperature for 15 min (TCT disappearance was monitored by thin-layer chromatography). In another flask, DMF (4.6 mL) was added to a stirred solution of 2-hydroxyacetophenone (3 mmol) in BF_3·Et_2O (7.5 mmol) at 10 °C for 5 min. The reaction mixture was then added to the white suspension containing TCT/DMF adduct dropwise and stirred at room temperature. After formation of clear solution, the reaction mixture was heated to 60 °C for 30–40 min and poured into boiling dilute HCl slowly and cooled. The solution was extracted with ethyl acetate (30 mL × 2) and the combined organic layer was dried over anhydrous Na_2SO_4. The crude obtained after evaporation of the solvent was chromatographed over silica gel column using chloroform–methanol mixtures as eluent to give **2a–2d**.

***4H-Chromen-4-one*[30] (2a) (*Table 1, entry 1*)**

Colorless solid; yield 306 mg (65%); mp 55–58 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.32 (d, *J* = 5.6 Hz, 1 H), 7.35–7.43 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 5.6 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 111.9, 117.2, 123.9, 124.3, 124.7, 132.8, 154.5, 155.5, 176.6. LC–MS: *m*/*z*: 147 [M + 1]$^+$. Anal. calcd. for $C_9H_6O_2$: C 73.97, H 4.14; found: C 73.94, H 4.19.

***7-Hydroxy-4H-chromen-4-one*[31] (2b) (*Table 1, entry 2*)**

Pale brown solid; yield 340 mg (70%); mp 206–208 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.21 (d, *J* = 6.0 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 6.0 Hz, 1H), 10.76 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 102.3, 111.9, 115.0, 117.0, 126.6, 156.0, 157.7, 162.5, 175.5. LC–MS: *m*/*z*: 161 [M – 1]$^-$. Anal. calcd. for $C_9H_6O_3$: C 66.67, H 3.73; found: C 66.65, H 3.75.

***7,8-Dihydroxy-4H-chromen-4-one*[31] (2c) (*Table 1, entry 3*)**

Brown solid; yield 402 mg (75%); mp 205–208 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.17 (d, *J* = 6.0 Hz, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 6.8 Hz, 1H), 8.19 (d, *J* = 6.0 Hz, 1H), 9.40 (s, 1H), 10.29 (S, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 111.3, 114.0, 115.0, 117.8, 132.9, 146.9, 150.0, 155.7, 176.0. LC–MS: *m*/*z*: 177 [M – 1]$^-$. Anal. calcd. for $C_9H_6O_4$: C 60.68, H 3.39; found: C 60.63, H 3.43.

***5,7-Dihydroxy-4H-chromen-4-one*[32] (2d) (*Table 1, entry 4*)**

Brown solid; yield 416 mg (78%); mp 268–270 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.20 (d, *J* = 2.0 Hz, 1H), 6.27 (d, *J* = 6.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 6.0 Hz, 1H), 10.85 (s, 1H), 12.69 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 93.9, 98.9, 104.8, 110.4, 149.8, 157.3, 157.7, 164.2, 181.2. LC–MS: *m*/*z*: 177 [M – 1]$^-$. Anal. calcd. for $C_9H_6O_4$: C 60.68, H 3.39; found: C 60.65, H 3.41.

General experimental procedure for isoflavones (9a–9h)

Method A

A mixture of substituted phenol (3 mmol), phenylacetic acid (3 mmol), and BF_3·Et_2O (15 mmol) was heated to 90 °C for 90 min under N_2. The reaction mixture was then cooled to 10 °C in an ice

bath and DMF (4.6 mL) was added dropwise. In another flask, 2,4,6-trichloro-1,3,5-triazine (TCT) (0.82 g, 4.5 mmol) was added to DMF (1 mL) and stirred at room temperature for 15 min (TCT disappearance was monitored by thin-layer chromatography). The above reaction mixture was then added dropwise to the white suspension containing TCT/DMF adduct at room temperature for 5 min. After formation of clear solution, the reaction mixture was heated to 60 °C for 30–40 min and poured into boiling dilute HCl slowly and cooled. The solution was extracted with ethyl acetate (30 mL × 2) and the organic layer was dried over anhydrous Na_2SO_4. The crude obtained after evaporation of the solvent was chromatographed over a silica gel column using chloroform–methanol mixtures as eluent to give isoflavones (**9a–9h**).

Method B

A mixture of substituted phenol (3 mmol), phenylacetic acid (3 mmol), and $BF_3{\cdot}Et_2O$ (9 mmol) was stirred to 80–90 °C for 90 min under N_2. The mixture was then poured into NaOAc solution (100 mL, 10%) and allowed to stand for 4 h and the solution extracted with EtOAc (3 × 100 mL). the combined organic layer was washed with water (20 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. The crude obtained after evaporation of the solvent was chromatographed over a silica gel column using hexane–EtOAc mixtures as eluent to give deoxybenzoins (**7f–7h**). The purified materials were then used for the synthesis of isoflavones. A mixture of deoxybenzoin (3 mmol) and $BF_3{\cdot}Et_2O$ (7.5 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-chromen-4-one*[14a] (9a) (*Table 2, entry 1*)**

Off-white solid; yield (method A) 621 mg (87%); mp 210–213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.88 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 2.4, 8.4 Hz, 1H), 7.34–7.44 (m, 3H), 7.57 (d, J = 7.2 Hz, 2H), 7.99 (d, J = 8.8 Hz,1H), 8.36 (s, 1H), 10.80 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 102.1, 115.2, 116.6, 123.5, 127.2, 127.6, 128.0, 128.8, 132.1, 153.6, 157.4, 162.6, 174.3. LC–MS: m/z: 237 [M – 1]$^-$. Anal. calcd. for $C_{15}H_{10}O_3$: C 75.62, H 4.23; found: C 75.60, H 4.27.

***7-Hydroxy-3-(3-methoxyphenyl)-4H-chromen-4-one* (9b) (*Table 2, entry 2*)**

Pale pink solid; yield (method A) 715 mg (89%); mp 215–217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.78 (s, 3H), 6.88 (s, 1H), 6.93–6.96 (m, 2H), 7.13–7.15 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 8.38 (s, 1H), 10.79 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.06, 102.1, 113.2, 114.6, 115.2, 116.6, 121.1, 123.3, 127.2, 129.0, 133.4, 153.8, 157.3, 159.0, 162.6, 174.3. LC–MS: m/z: 267 [M – 1]$^-$. Anal. calcd. for $C_{16}H_{12}O_4$: C 71.64, H 4.51; found: C 71.60, H 4.56.

***7-Hydroxy-3-(4-methoxyphenyl)-4H-chromen-4-one*[27] (9c) (*Table 2, entry 3*)**

Off-white solid; yield (method A) 723 mg (90%); mp 257–258 °C. ^{1}H NMR, (400 MHz, DMSO-d_6) δ: 3.78 (s, 3H), 6.88 (d, J = 2 Hz, 1H), 6.94 (dd, J = 2.4, 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 1H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.1, 102.0, 113.6, 114.1, 115.0, 116.6, 123.1, 124.1, 127.2, 130.0, 153.0, 157.4, 158.9, 162.3, 174.6. LC–MS: m/z: 267 [M – 1]$^-$. Anal. calcd. for $C_{16}H_{12}O_4$: C 71.64, H 4.51; found: C 71.60, H 4.55.

***7-Hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one*[28] (9d) (*Table 2, entry 4*)**

Pale brown powder; yield (method A) 670 mg (88%); mp 310–312 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.79 (d, J = 8.4, 2H), 6.83 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 2.0, 8.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2 H), 7.96 (d, J = 8.0 Hz, 1H), 8.28 (s, 1H), 9.55 (s, 1H), 10.83 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 102.0, 114.9, 115.1, 122.5, 123.5, 127.2, 130.0, 157.2, 157.3, 162.4, 174.7. LC–MS: m/z: 253 [M – 1]$^-$. Anal. calcd. for $C_{15}H_{10}O_4$: C 70.86, H 3.96; found: C 70.85, H 3.98.

***7-Hydroxy-3-(2,4-dimethoxyphenyl)-4H-chromen-4-one* (9e) (*Table 2, entry 5*)**

Off-white solid; yield (method A) 760 mg (85%); mp 265–270 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.70 (s, 3H), 3.80 (s, 3H), 6.56 (d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 6.86 (s, 1H), 6.93 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 8.11 (s, 1H), 10.73 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.2, 55.5, 98.6, 102.1, 104.6, 113.5, 114.9, 116.5, 121.5, 127.1, 132.0, 153.8, 157.4, 158.4, 160.6, 162.4, 174.3. LC–MS: m/z: 297 [M – 1]$^-$. Anal. calcd. for $C_{17}H_{14}O_5$: C 68.45, H 4.73; found: C 68.46, H 4.75.

***7,8-Dihydroxy-3-phenyl-4H-chromen-4-one* (9f) (*Table 2, entry 6*)**

Pale brown solid; yield (method A) 594 mg (78%), yield (method B) 670 mg (88%); mp 200–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.98 (d, J = 8.8 Hz, 1H), 7.37–7.44 (m, 3H), 7.49 (d, J = 8.8 Hz, 1H), 7.59–7.57 (m, 2H), 8.43 (s, 1H), 9.46 (s, 1H) 10.33 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 114.2, 115.6, 117.4, 123.0, 127.5, 128.0, 128.9, 132.2, 132.9, 146.7, 150.1, 153.5, 174.8. LC–MS: m/z: 253 [M – 1]$^-$. Anal. calcd. for $C_{15}H_{10}O_4$: C 70.86, H 3.96; found: C 70.84, H 4.00.

***7,8-Dihydroxy-3-(3-methoxyphenyl)-4H-chromen-4-one* (9g) (*Table 2, entry 7*)**

Brown solid; yield (method A) 640 mg (75%), yield (method B) 725 mg (85%); mp 216–218 °C. ^{1}H NMR, (400 MHz, DMSO-d_6) δ: 3.78 (s, 3H), 6.94 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 7.14–7.17 (m, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 8.44 (s, 1H), 9.41 (s, 1H), 10.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.0, 113.1, 114.2, 114.7, 115.7, 117.4, 121.2, 122.7, 129.0, 132.9, 133.5, 146.6, 150.1, 153.6, 158.9, 174.7. LC–MS: m/z: 283 [M – 1]$^-$. Anal. calcd. for $C_{16}H_{12}O_5$: C 67.60, H 4.25; found: C 67.58, H 4.28.

***7,8-Dihydroxy-3-(4-methoxyphenyl)-4H-chromen-4-one*[29] (9h) (*Table 2, entry 8*)**

Pale brown solid; yield (method A) 640 mg (75%), yield (method B) 760 mg (89%); mp 252–254 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.79 (s, 3H), 6.96 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 8.38 (s, 1H), 9.42 (s, 1H), 10.29 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ: 55.1, 113.5, 114.1, 115.6, 117.4, 122.6, 124.4, 130.0, 132.8, 146.7, 149.8, 150.0, 152.8, 158.9, 175.0. LC–MS: m/z: 283 [M – 1]$^-$. Anal. calcd. for $C_{16}H_{12}O_5$: C 67.60, H 4.25; found: C 67.59, H 4.28.

General experimental procedure for homo-isoflavones (10a–10f)

Method A

A mixture of substituted phenol (3 mmol), 3-phenylpropanoic acid (3 mmol), and $BF_3{\cdot}Et_2O$ (15 mmol) was heated to 90 °C for 90 min under N_2. The reaction mixture was then cooled to 10 °C and DMF (4.6 mL) was added dropwise. In another flask, 2,4,6-trichloro-1,3,5-triazine (TCT) (0.82 g, 4.5 mmol) was added to DMF (1 mL) and stirred at room temperature for 15 min (TCT disappearance was monitored by thin-layer chromatography). The above reaction mixture was then added dropwise to the white suspension containing TCT/DMF adduct at room temperature for 5 min. After formation of clear solution, the reaction mixture was heated to 60 °C for 30–40 min and poured into boiling dilute HCl slowly and cooled. The solution was extracted with ethyl acetate (30 mL × 2) and the organic layer was dried over anhydrous Na_2SO_4. The crude obtained after evaporation of the solvent was chromatographed over a silica gel column using chloroform–methanol mixtures as eluent to give isoflavones (**10a–10h**).

Method B

A mixture of substituted phenol (3 mmol), 3-phenylpropanoic acid (3 mmol), and $BF_3{\cdot}Et_2O$ (9 mmol) was stirred to 80–90 °C for 90 min under N_2. The mixture was then poured into NaOAc solution (100 mL, 10%) and allowed to stand for 4 h and the solution extracted with EtOAc (3 × 100 mL). The combined organic layer

was washed with water (20 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. The crude obtained after evaporation of the solvent was chromatographed over a silica gel column using hexane–EtOAc mixtures as eluent to give dihydrochalcones (**8d–8f**). The purified materials were then used for the synthesis of homoisoflavones. A mixture of dihydrochalcone (3 mmol) and $BF_3{\cdot}Et_2O$ (7.5 mmol) was cooled to 10 °C and DMF (4.6 mL) was added dropwise. The cyclization procedure and workup are similar to method A.

***3-Benzyl-7-hydroxy-4H-chromen-4-one*[33] (10a) (*Table 3, entry 1*)**

Pale pink solid; yield (method A) 620 mg (82%); mp 210–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.67 (s, 2H), 6.82 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 2.4, 8.8 Hz, 1H) 7.14–7.18(1H), 7.23–7.29 (m, 4 H), 7.87 (d, J = 8.8 Hz, 1H), 8.17 (s, 1H), 10.72 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 30.6, 102.1, 114.9, 116.2, 122.8, 125.9, 126.7, 128.1, 128.4, 139.7, 153.2, 157.7, 162.4, 175.4. LC–MS: m/z: 251 [M – 1]$^-$. Anal. calcd. for $C_{16}H_{12}O_3$: C 76.18, H 4.79; found: C 76.14, H 4.82.

***7-Hydroxy-3-(4-methoxybenzyl)-4H-chromen-4-one*[19] (10b) (*Table 3, entry 2*)**

Pale brown solid; yield (method A) 720 mg (85%); mp 161–165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.59 (s, 2H), 3.69 (s, 3H), 6.81–6.83 (m, 3H) 6.89 (dd, J = 2.0, 8.8 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2 H), 7.87 (d, J = 8.8 Hz, 1H), 8.12(s, 1H), 10.71 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.8, 54.9, 102.1, 113.6, 114.9, 116.2, 123.3, 126.7, 129.0, 129.5, 131.5, 153.0, 157.6, 157.7, 162.4, 175.4. LC–MS: m/z: 281 [M – 1]$^-$. Anal. calcd. for $C_{17}H_{14}O_4$: C 72.33, H 5.00; found: C 72.30, H 5.05.

***7-Hydroxy-3-(4-hydroxybenzyl)-4H-chromen-4-one*[19] (10c) (*Table 3, entry 3*)**

Colorless solid; yield (method A) 707 mg (88%); mp 210–212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.52 (s, 2H), 6.64 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 8.8, 2.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.8 Hz, 1H), 8.05 (s, 1 H), 9.85 (s, 1H), 10.75 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 30.2, 102.1, 114.5, 115.1, 116.3, 123.9, 126.7, 128.9, 129.4, 152.3, 155.5, 157.8, 162.3, 176.3. LC–MS: m/z: 267 [M – 1]$^-$. Anal. calcd. for $C_{16}H_{12}O_4$: C 71.64, H 4.51; found: C 71.62, H 4.54.

***7-Hydroxy-3-(2,5-dimethoxybenzyl)-4H-chromen-4-one* (10d) (*Table 2, entry 4*)**

Light brown solid; yield (method A) 795 mg (85%); mp 184–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.59 (s, 2H), 3.69 (s, 3H), 3.75 (s, 3H), 6.70–6.75 (m, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.90 (dd, J = 2.0, 8.8 Hz, 1H),7.88 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 10.68 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 25.2, 55.2, 55.7, 102.1, 111.3, 111.6, 114.9, 116.1, 116.4, 121.7, 126.7, 128.0, 151.1, 151.2, 152.9, 153.2, 157.7, 162.4, 175.4. LC–MS: m/z: 311 [M – 1]$^-$. Anal. calcd. for $C_{18}H_{16}O_5$: C 69.22, H 5.16; found: C 69.19, H 5.19.

***7,8-Dihydroxy-3-(4-methoxybenzyl)-4H-chromen-4-one*[19] (10e) (*Table 2, entry 5*)**

Colorless solid; yield (method A) 670 mg (75%), yield (method B) 768 mg (86%); mp 250–253 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.60 (s, 2H), 3.68 (s, 3H), 6.81 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 1H), 8.19 (s, 1H), 9.34 (s,1H), 10.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.8, 54.9, 113.6, 114.0, 115.1, 117.1, 122.7, 129.4, 131.6, 132.8, 147.0, 149.8, 152.8, 157.6, 175.9. LC–MS: m/z: 297 [M – 1]$^-$. Anal. calcd. for $C_{17}H_{14}O_5$: C 68.45, H 4.73; found: C 68.42, H 4.79.

***7,8-Dihydroxy-3-(2,5-dimethoxybenzyl)-4H-chromen-4-one* (10f) (*Table 2, entry 6*)**

Pale brown solid; yield (method A) 767 mg (78%), yield (method B) 836 mg (85%); mp 226–230 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.60 (s, 2H), 3.64 (s, 3H), 3.75 (s, 3H), 6.72–6.75 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.98 (s, 1 H), 9.32 (s, 1H),10.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 25.2, 55.2, 55.8, 111.3, 111.5, 114.0, 115.1, 116.4, 116.9, 121.1, 128.1, 132.8, 147.0, 149.8, 151.2, 152.9, 153.0, 175.9. LC–MS: m/z: 327 [M – 1]$^-$. Anal. calcd. for $C_{18}H_{16}O_6$: C 65.85, H 4.91; found: C 65.81, H 4.96.

Supplementary material

Supplementary data (^{1}H NMR and ^{13}C NMR spectra of all synthesized compounds) are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2013-0137.

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