Chemistry of Heterocyclic Compounds, Vol. 43, No. 2, 2007

MICROWAVE-PROMOTED AUTOMATED SYNTHESIS OF A COUMARIN LIBRARY

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A 30-membered library of coumarins has been synthesized in a microwave-assisted Pechmann reaction using neat trifluoroacetic acid both as an acidic reagent and a reaction medium. Alternatively, polymer-supported sulfonic acid Amberlyst-15 could also be employed to facilitate the formation of coumarins. The use of a specially-built microwave synthesizer with liquid handling tools rendered the automated synthesis of a coumarin library feasible.

Keywords: coumarin, microwave promoted synthesis, library synthesis.

The development of new methods for synthesis of libraries of heterocyclic compounds is an important topic in combinatorial chemistry. The microwave technology is particularly suitable for the rapid and automated production of heterocyclic libraries. Thus, microwave irradiation enables organic chemists to reduce the time of heterocycle synthesis from days and hours to minutes and even seconds [1-3]. In addition, suppressed formation of side-products and improved yields has frequently been observed under microwave heating conditions. Finally, the proper choice of microwave processing techniques (solvent-free, solid- or polymer-supported conditions) can simplify the workup and avoid laborious and time-consuming purification of the target heterocycle. Herein we report a convenient microwave-promoted solution-phase synthesis of a 30-membered library of coumarins using a specially-built microwave synthesizer with automation tools.

The coumarin heterocycle is a common motif in a number of natural products [4], pharmaceuticals, fragrances, and agrochemicals [5, 6]. Among various synthetic approaches toward coumarins, the cyclocondensation of phenol with β-keto esters under acid-catalyzed conditions (Pechmann reaction) [7] is especially suited for the production of a heterocycle library because high structural diversity in the coumarins can be introduced in a single synthetic step simply by proper variation of precursors. The Pechmann cyclization requires the presence of various acids such as H_2SO_4 [8], CF_3CO_2H [9], sulfonic acid resin [10], P_2O_5 [11], and $AlCl_3$ [12]. Prolonged reaction times (up to 24 h at ambient temperature) or heating above 150°C usually is necessary to bring the reaction to completion, indicating that microwave dielectric heating could be beneficial. Indeed, substantial acceleration of the Pechmann reaction in a household microwave oven was observed in the presence of various catalysts such as H_2SO_4 [13], task-specific ionic liquids [14] as well as solid acid catalysts such as P_2O_5/molecular sieves [15] and montmorillonite K10/graphite [16].

Recently, solvent-free synthesis of coumarins has been successfully carried out using short pulses of microwave irradiation to initiate the exothermic Pechmann cyclocondensation [17].

Synthetic procedures developed for household microwave ovens frequently could not be reproduced on dedicated single-mode microwave equipment. Furthermore, methodologies for automated production of libraries usually employ liquid handling tools, which are incompatible with solvent-free conditions. Therefore we

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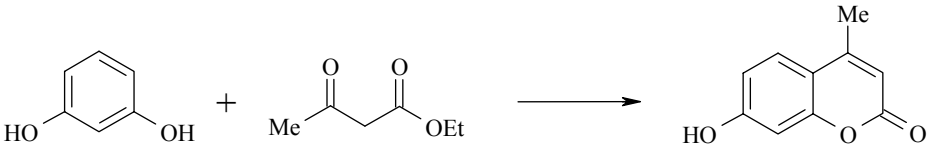
envisioned that development of a method for automated solution-phase synthesis of a coumarin library would be highly desirable. The Pechmann reaction between resorcinol (**1a**) and ethyl acetoacetate (**2a**) was chosen as a model to identify the most suitable cyclization conditions, and the yields of the coumarin **3aa** were determined by HPLC assay (Table 1).



1a **2a** **3aa**

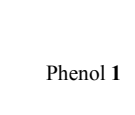
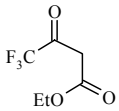
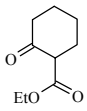
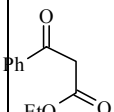
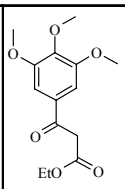
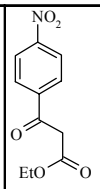
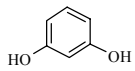
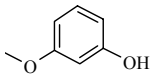
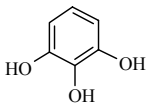
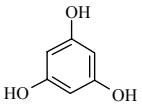
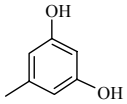
Montmorillonite K10 clay in benzotrifluoride afforded the desired coumarin **3** in moderate yields (Table 1, entry 1). The use of Lewis acids did not improve the outcome (entries 2 and 3), while P_2O_5 and *p*-toluenesulfonic acid in toluene were completely inefficient (entries 4 and 5). On the contrary, coumarin **3** was formed in high yields in the presence of camphorsulfonic acid and trifluoroacetic acid (entries 6 and 7). These results prompted us to examine polymer-supported sulfonic acid because under microwave flash heating conditions slow heterogeneous solid-phase reactions could be efficiently accelerated without any degradation of the polymer backbone [18]. To our delight, heterocycle **3** was formed in 72% yield (entry 8) in the presence of Amberlyst-15. The latter conditions are especially useful for the automated library production because the acid catalyst could be conveniently removed from the reaction mixture simply by decanting or filtration. Additional trials showed that neat Brønsted acids such as H_2SO_4, H_3PO_4, and acetic acid were inefficient (entries 9-11). Eventually, the highest yields of the desired coumarin **3** were obtained using neat trifluoroacetic acid (entry 12). With two alternative conditions for the microwave-assisted Pechmann synthesis established (Method A: neat trifluoroacetic acid and Method B: Amberlyst-15 in toluene), a 30-membered library of coumarins was prepared using a subset of five phenols and six β-keto esters (Table 2).

TABLE 1. Evaluation of the Pechmann reaction conditions

Entry	Catalyst	Amount	Solvent	Time, min	Temperature, °C	HPLC yield, %
1	Montmorillonite K-10	200 mg	$PhCF_3$	10	120	37
2	$AlCl_3$	2 eq	$PhNO_2$	10	120	30
3	$FeCl_3$	2 eq	Toluene	10	120	43
4	P_2O_5	2.5 eq	Toluene	15	120	5
5	*p*-Toluenesulfonic acid	2 eq	Toluene	15	120	0
6	Camphorsulfonic acid	2 eq	Toluene	15	120	62
7	CF_3COOH	10%	Toluene	20	120	55
8	Amberlyst-15	100 mg	Toluene	30	100	72*
9	—	—	H_2SO_4	30	100	33*
10	—	—	H_3PO_4	30	100	18
11	—	—	AcOH	30	120	0
12	—	—	CF_3COOH	30	100	89*

* Isolated yields.

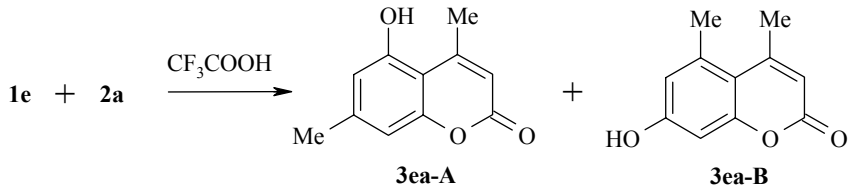
TABLE 2. Synthesis and Yields* of a Library of Coumarins Using the Pechmann Reaction

Phenol **1**	β-Keto ester **2**					
	 **2a**	 **2b**	 **2c**	 **2d**	 **2e**	 **2f**
 **1a**	**3aa** 89 (72)	**3ab** 50 (20)	**3ac** 95 (79)	**3ad** 84 (69)	**3ae** 46	**3af** 81 (10)
 **1b**	**3ba** 90 (60)	**3bb** 63 (10)	**3bc** 99 (32)	**3bd** 36 (12)	**3be** 24	**3bf** 37
 **1c**	**3ca** 70 (76)	**3cb** 20	**3cc** 87 (52)	**3cd** 71 (61)	**3ce** –	**3cf** 66
 **1d**	**3da** 90 (32)	**3db** 25	**3de** 99 (24)	**3dd** 76 (66)	**3de** 60	**3df** 52
 **1e**	**3ea** 71 (41)	**3eb** –	**3ec** 76	**3ed** 22	**3ee** 15	**3ef** 50

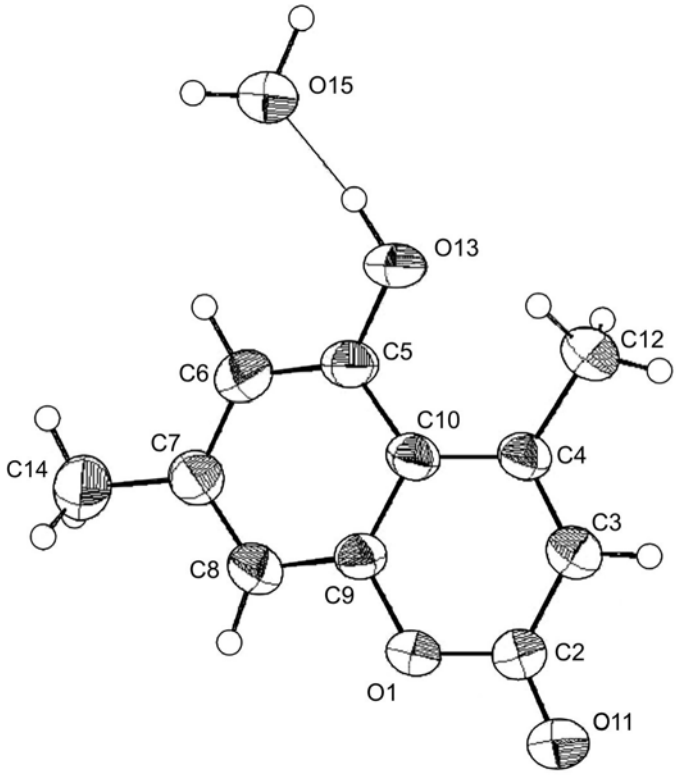
* Isolated yields of coumarins synthesized by Method A (Method B). Method A: CF_3COOH, MW (30 min, 100ºC); Method B: Amberlyst-15, toluene, MW (30 min, 100ºC), in parentheses.

Generally, the use of Method A afforded coumarins **3** in higher yields and with better reproducibility than in the case of Method B. The large variations in yields under both established microwave procedures could be attributed to the diverse reactivity of various phenols and β-keto esters. Nevertheless, the target heterocycles were readily obtained in moderate to excellent yields, and only two experiments failed to afford any of the corresponding coumarins **3ce** and **3eb**. Given the simplicity of workup (filtration of the product after addition of water in the case of Method A and removal of solid supported acid, followed by concentration in the case of Method B), the microwave-assisted methodology does constitute a rapid and convenient method for the production of a coumarin library. Furthermore, the established conditions are especially suited for automation. Thus, β-keto esters could be delivered to reaction vials from stock solutions in trifluoroacetic acid, using a robotic arm and liquid handling tools of the microwave synthesizer.* The resulting reaction mixture could then be automatically transferred to the microwave cavity, heated, and withdrawn from the dielectric heating area. As a result, the whole process of library generation (from mixing of the reagents till the workup) could be performed automatically, in an unattended manner.

The reaction of 5-methylresorcinol **1e** with ethyl acetoacetate **2a** (Scheme 1) deserves special comment because of the controversy in the literature regarding the structure of the product coumarin **3ea**. Thus, two different regioisomers **3ea-A** [19–22] and **3ea-B** [15, 23, 24] have been reported as the major product in the Pechmann condensation.



We observed the formation of a single regioisomer in 71% yield by using method A. The structure of coumarin **3ea-A** was unambiguously established by X-ray structure analysis (Fig. 1). The formation of coumarin **3ea-A** evidently could be rationalized by electronic effects. Thus, quantum-chemical calculations using the semi-empirical AM1 method [25] demonstrated that the C(2) atom possesses higher negative net atomic charge (-0.3055) and higher electron density (4.3055) than the competitive C(4) or C(6) positions (-0.1943 and 4.1943, respectively). Assuming that the initial step of the Pechmann synthesis is a Friedel-Crafts type acylation of resorcinol **1e** with the enol form of β-keto ester **2a** [26], electrophilic aromatic substitution will occur at the more nucleophilic C(2) position.



X-ray structure of coumarin **3ea-A**.

* A purpose-built automated microwave equipment, Smith Synthesizer by Personal Chemistry, with liquid handling tools and robotic arm has been employed for synthesis of the library of coumarins.

EXPERIMENTAL

Microwave heating was performed on a specially-built Smith Synthesizer by Personal Chemistry (Uppsala, Sweden) with a monomode cavity and temperature control. Melting points were obtained on an OptiMelt apparatus and are uncorrected. NMR spectra were observed on a Varian Mercury 200 spectrometer (200, 188 and 50 MHz for ^{1}H, ^{19}F and ^{13}C respectively), in $CDCl_3$ (compounds **3aa**, **ba–bc**) and DMSO-d_6 (compounds **3ab–af**, **bd–bf**, **ca–cf**, **da–df**, **ea–ef**), with tetramethylsilane as an internal standard and $CFCl_3$ for ^{19}F. GC-MS spectra were obtained on Hewlett Packard 5890 II apparatus with an HP 5971 mass-detector. Reactions were monitored by thin-layer chromatography on Merck Kieselgel 60_{F254}.

Synthesis of coumarins 3aa–3ef (General Procedure). A. An oven dried Emrys^{TM} MW process vial (2-5 ml) equipped with a Teflon-coated stirring bar was charged with phenol **1** (1.0 mmol) and ethyl β-ketocarboxylate **2** (1.0 mmol) and closed using an aluminum open-top seal with a PTFE-faced septum. Trifluoroacetic acid (0.5 ml) was introduced *via* a syringe and the reaction mixture was microwave-irradiated for 30 min at 100°C. After cooling, the reaction mixture was gradually poured into intensely stirred ice cold water (15 ml). Filtration of the formed precipitate and recrystallization from the appropriate solvent afforded coumarin **3**.

A (automated procedure). An oven-dried Emrys^{TM} MW process vial (2–5 ml) equipped with a Teflon-coated stirring bar was charged with phenol **1** (1.0 mmol) and closed using an aluminum open-top seal with a PTFE-faced septum. Ethyl β-ketocarboxylate (0.5 ml of 2M stock solution in trifluoroacetic acid) was added to the reaction vial by the liquid handling tool of the microwave synthesizer. The process vial was then placed in the microwave cavity by a robotic Z-arm and irradiated for 30 min at 100°C. After cooling, the reaction mixture was gradually poured into intensely stirred ice cold water (15 ml). Filtration of the formed precipitate and recrystallization from the appropriate solvent afforded coumarin **3**.

B. An oven-dried Emrys^{TM} MW process vial (2–5 ml) equipped with a Teflon-coated stirring bar was charged with phenol **1** (1.0 mmol), ethyl β-ketocarboxylate **2** (1.0 mmol), and Amberlyst-15 (100 mg) and closed using an aluminum open-top seal with a PTFE-faced septum. Toluene (0.5 ml) was introduced *via* a syringe and the reaction mixture was microwave-irradiated for 30 min at 100°C. After cooling, the reaction mixture was diluted with ethanol until all the precipitate was dissolved. Amberlyst-15 was removed by filtration and the filtrate was concentrated *in vacuo* (aspirator). Recrystallization of the residue from the appropriate solvent afforded coumarin **3**.

7-Hydroxy-4-methylchromen-2-one (**3aa**). Yellowish needles, mp 188–190ºC (recrystal- lized from EtOH–H_2O) (lit. [27] 185ºC), R_f 0.53 (dichloromethane–methanol, 10:1). ^{1}H NMR, δ, ppm (*J*, Hz): 7.50 (1H, d, *J* = 8.5); 7.00 (1H, d, *J* = 2.1); 6.98 (1H, br s); 6.87 (1H, dd, *J* = 8.5 and *J* = 2.1); 6.15 (1H, d, *J* = 0.9); 2.41 (3H, d, *J* = 0.9). GC–MS, *m/z* (I_{rel}, %): 176 (64), 148 (100).

7-Hydroxy-4-trifluoromethylchromen-2-one (**3ab**). Off-white crystals, mp 183–184ºC (recrystallized from EtOH–H_2O) (lit. [28] 184-185ºC), R_f 0.39 (dichloromethane–methanol, 10:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.93 (1H, s); 7.50 (1H, d, *J* = 9.0); 6.78 (1H, s); 6.85 (1H, d, *J* = 9.0); 6.78 (1H, s); 6.71 (1H, s). ^{19}F NMR (DMSO-d_6), δ: -64.0. GC–MS, *m/z* (I_{rel}, %): 230 (75), 202 (100).

3-Hydroxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (**3ac**). Yellow crystals, mp 200-202ºC (recrystallized from EtOH–H_2O) (lit. [29] 203–204ºC), R_f 0.52 (dichloromethane–methanol, 10:1). ^{1}H NMR, δ, ppm (*J*, Hz): 7.45 (1H, d, *J* = 9.0); 7.10 (1H, s); 7.01 (1H, d, *J* = 2.6); 6.84 (1H, dd, *J* = 9.0 and *J* = 2.6); 2.79-2.74 (2H, m); 2.59-2.55 (2H, m); 1.87-1.81 (4H, m). GC–MS, *m/z* (I_{rel}, %): 216 (100), 201 (52), 160 (60).

7-Hydroxy-4-phenylchromen-2-one (**3ad**). Off-white crystals, mp 242-244ºC (recrystallized from EtOH–H_2O) (lit. [30] 244ºC), R_f 0.54 (dichloromethane–methanol, 10:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.85 (1H, s); 7.55-7.52 (5H, m); 7.25 (1H, d, *J* = 8.4); 6.78 (1H, s); 6.76 (1H, d, *J* = 8.4); 6.13 (1H, s). GC–MS, *m/z* (I_{rel}, %): 238 (90), 210 (100), 201 (40), 181 (45).

7-Hydroxy-4-(3,4,5-trimethoxyphenyl)chromen-2-one (**3ae**). Off-white crystals, mp 259-260ºC (recrystallized from EtOH) (lit. [31] 253ºC), R_f 0.26 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.62 (1H, br s); 7.43 (1H, d, *J* = 9.4); 6.82-6.72 (4H, m); 6.19 (1H, s); 3.80 (6H, s); 3.71 (3H, s).

7-Hydroxy-4-(4-nitrophenyl)chromen-2-one (**3af**). Yellow crystals, mp >350ºC (lit. [32] decomp. >360ºC), R_f 0.33 (petroleum ether–EtOAc, 5:2). ^{1}H NMR, δ, ppm (*J*, Hz): (1H, s); 8.41-8.31 (2H, m); .84-7.72 (2H, m); 7.17 (1H, d, *J* = 8.5); 6.81 (1H, d, *J* = 2.2); 6.76 (1H, dd, *J* = 8.5, *J* = 2. 2); 6.25 (1H, s).

7-Methoxy-4-methylcromen-2-one (**3ba**). White crystals, mp 156-157ºC (recrystallized from EtOH) (lit. [30] 159ºC), R_f 0.79 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 7.49 (1H, d, *J* = 8.4); 6.68 (1H, dd, *J* = 8.4 and *J* = 2.6); 6.81 (1H,d, *J* = 2.6); 6.13 (1H, d, *J* = 1.0); 3.87 (3H, s); 2.39 (3H, d, *J* = 1.0). GC–MS, *m/z* (I_{rel}, %): 190 (82), 162 (88), 147 (100).

7-Methoxy-4-trifluoromethylcromen-2-one (**3bb**). White crystals, mp 113-114ºC (recrystallized from EtOH–H_2O) (lit. [33] 112ºC), R_f 0.71 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 7.63 (1H, dq, *J* = 8.7 and $J_{H–F}$ = 1.8); 6.92 (1H, dd, *J* = 8.7 and *J* = 2.6); 6.88 (1H, d, *J* = 2.6); 6.62 (1H, s); 3.90 (3H, s). ^{19}F NMR (DMSO-d_6), δ -65.1. GC–MS, *m/z* (I_{rel}, %): 244 (65), 216 (67), 201 (100).

3-Methoxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (**3bc**). Yellow crystals, mp 119-120ºC (recrystallized from EtOH–H_2O) (lit. [34] 121ºC), R_f 0.65 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 7.45 (1H, d, *J* = 8.5); 6.83 (1H, dd, *J* = 8.5 and *J* = 2.5); 6.80 (1H, d, *J* = 2.5); 3.86 (3H, s), 2.77-2.74 (2H, m); 2.56–2.53 (2H, m); 1.87-1.81 (4H, m). GC–MS, *m/z* (I_{rel}, %): 230 (100), 215 (53), 202 (46), 174 (53).

7-Methoxy-4-phenylchromen-2-one (**3bd**). Off-white crystals, mp 108-109ºC (lit. [35] 110-111ºC), R_f 0.66 (petroleum ether–EtOAc, 5:2). ^{1}H NMR, δ, ppm (*J*, Hz): 7.61-7.46 (5H, m); 7.33 (1H, d, *J* = 8.8); 7.08 (1H, d, *J* = 2.5); 6.92 (1H, dd, *J* = 8.8, *J* = 2.5); 6.22 (1H, s); 3.85 (3H, s).

7-Methoxy-4-(3,4,5-trimethoxyphenyl)chromen-2-one (**3be**). Colorless crystals, mp 209-210ºC (lit. [36] 172-175ºC (AcOH)), R_f 0.52 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 7.52 (1H, d, *J* = 8.8); 7.07 (1H, d, *J* = 2.5); 6.92 (1H, dd, *J* = 8.8, *J* = 2.5); 7.80 (2H, s); 6.19 (1H, s); 6.28 (1H, s); 3.85 (3H, s); 3.80 (6H, s); 3.72 (3H, s).

7-Methoxy-4-(4-nitrophenyl)chromen-2-one (**3bf**). Grey crystals, mp 210-211ºC, R_f 0.62 (petroleum ether–EtOAc, 5:2). ^{1}H NMR, δ, ppm (*J*, Hz): 8.43-8.33 (2H, m); 7.85-7.75 (2H, m); 7.25 (1H, d, *J* = 8.9); 7.12 (1H, d, *J* = 2.6); 6.92 (1H, dd, *J* = 8.9, *J* = 2.6); 6.35 (1H, s); 3.86 (3H, s). Found, %: C 64.30; H 3.59; N 4.68. $C_{16}H_{11}NO_5$. Calculated, %: C 64.65; H 3.73; N 4.71.

7,8-Dihydroxy-4-methylcromen-2-one (**3ca**). Brownish crystals, mp 227-229ºC (recrystallized from acetone–H_2O) (lit. [30] 235ºC), R_f 0.27 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.37 (1H, br s); 9.26 (1H, br s); 7.07 (1H, d, *J* = 8.4); 6.79 (1H, d, *J* = 8.4); 6.09 (1H, d, *J* = 1.1); 2.32 (3H, d, *J* = 1.1).

7,8-Dihydroxy-4-trifluoromethylchromen-2-one (**3cb**). Brownish crystals, mp 202-203ºC (lit. [29] 222-223ºC), R_f 0.26 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.51 (1H, br s); 9.59 (1H, br s); 7.04 (1H, dq, *J* = 8.8, *J* = 2.1); 6.90 (1H, d, *J* = 8.8); 6.71 (1H, s).

3,4-Dihydroxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (**3cc**). Dark yellow crystals, mp 254-256ºC (recrystallized from EtOH–H_2O) (lit. [37] 269–276ºC), R_f 0.31 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 9.82 (1H, br s); 9.19 (1H, br s); 7.00 (1H, d, *J* = 8.4); 6.76 (1H, d, *J* = 8.4); 2.69–2.67 (2H, m); 2.41-2.35 (2H, m); 1.72-1.70 (4H, m).

7,8-Dihydroxy-4-phenylchromen-2-one (**3cd**). Brown needles, mp 191-193ºC (recrystallized from EtOH–H_2O) (lit. [9] 195-197ºC), R_f 0.24 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 7.57-7.40 (5H, m); 6.99 (1H, d, *J* = 8.8); 6.86 (1H, d, *J* = 8.8); 6.22 (1H, s).

7,8-Dihydroxy-4-(4-nitrophenyl)chromen-2-one (**3cf**). Yellow crystals, mp 291-294ºC (recrystallized from EtOH–H_2O) (lit. [32] 278ºC), R_f 0.19 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 8.40-8.28 (2H, m); 7.83-7.70 (2H, m); 6.77 (1H, d, *J* = 8.8); 6.63 (1H, d, *J* = 8.8); 6.22 (1H, s).

5,7-Dihydroxy-4-methylchromen-2-one (**3da**). Yellowish crystals, mp 280-285ºC (decomp.) (recrystallized from EtOH–H_2O) (lit. [38] 282-284ºC), R_f 0.31 (dichloromethane–methanol, 10:1). ^{1}H NMR, δ, ppm: 10.51 (1H, s); 10.28 (1H, s); 6.24 (1H, s); 6.15 (1H, s); 5.74 (1H, s); 3.33 (3H, s).

6,8-Dihydroxy-4-trifluoromethylchromen-2-one (**3db**). Yellow crystals, mp 254-255ºC (lit. [28] 255-257ºC), R_f 0.14 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.90 (1H, br s); 10.65 (1H, br s); 6.51 (1H, s); 6.30 (1H, d, *J* = 2.2); 6.27 (1H, d, *J* = 2.2).

2,4-Dihydroxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (**3dc**). White crystals, mp 258-260ºC (recrystallized from EtOH–H_2O) (lit. [39] 258ºC), R_f 0.16 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.32 (1H, s); 10.07 (1H, s); 6.22 (1H, d, *J* = 2.5); 6.12 (1H, d, *J* = 2.5); 3.07–2.95 (2H, m); 2.39-2.26 (2H, m); 1.74-1.53 (4H, m).

5,7-Dihydroxy-4-phenylchromen-2-one (**3dd**). Yellowish crystals, mp 208-210ºC (recrystallized from EtOH–H_2O) (lit. [40] 234-235ºC), R_f 0.34 (dichloromethane–methanol, 10:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.39 (1H, br s); 10.10 (1H, s); 7.38-7.29 (5H, m); 6.25 (1H, d, *J* = 2.0); 6.14 (1H, d, *J* = 2.0); 5.72 (1H, s).

5,7-Dihydroxy-4-(3,4,5-trimethoxyphenyl)chromen-2-one (**3de**). Brown crystals, mp 212-213ºC (decomp.) (lit. [36] 245-247ºC), R_f 0.22 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.50 (1H, br s); 10.23 (1H, s); 6.62 (2H, s); 6.26 (1H, d, *J* = 2.2); 6.22 (1H, d, *J* = 2.2); 5.82 (1H, s); 3.75 (6H, s); 3.63 (3H, s).

5,7-Dihydroxy-4-(4-nitrophenyl)chromen-2-one (**3df**). Light brown crystals, mp 266ºC (decomp.) (lit. [32] decomp.>260ºC), R_f 0.22 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.49 (1H, s); 10.28 (1H, s); 8.24–8.19 (2H, m); 7.63-7.59 (1H, s); 6.28 (1H, d, *J* = 2.2); 6.15 (1H, d, *J* = 2.2); 5.84 (1H, s).

5-Hydroxy-4,7-dimethylchromen-2-one (**3ea**). Brownish needles, mp 245-247ºC (recrystallized from EtOH–H_2O) (lit. [41] 248-250ºC), R_f 0.41 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.56 (1H, br s); 6.65 (1H, s); 6.59 (1H, s); 6.08 (1H, d, *J* = 0.8); 2.56 (3H, d, *J* = 0.8); 2.30 (3H, s). ^{13}C NMR (DMSO-d_6), δ, ppm: 159.8d, C(2)), 156.4 (m, C(5)), 154.8-154.5 (m, C(4 and 9)), 142.7 (ddq, C(7)), 111.9 (qdd, C(6)), 111.8 (dq, C(3)), 107.7 (qdd, C(8)), 106.5 (m, C(10)), 23.5 (dq, C(12)), 21.1 (tq, C(14)). NMR signals assigned by CH correlation. GC–MS, *m/z* (I_{rel}, %): 190 (56), 162 (100), 161 (66).

1-Hydroxy-3-methyl-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (**3ec**). Yellow crystals, mp 241-243ºC (lit. [42] 243-245ºC), R_f 0.39 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm: 10.33 (1H, s); 6.59-6.55 (1H, m); 6.55–6.50 (1H, m); 3.10-2.99 (2H, m); 2.41-2.30 (2H, m); 2.23 (3H, s); 1.70-1.59 (4H, m).

5-Hydroxy-7-methyl-4-phenylchromen-2-one (**3ed**). Off-white crystals, mp 217-219ºC (lit. [9] 226ºC), R_f 0.52 (petroleum ether–EtOAc, 5:2). ^{1}H NMR, δ, ppm (*J*, Hz): 10.12 (1H, s); 7.40-7.27 (5H, m); 6.70 (1H, d, *J* = 0.9); 6.45 (1H, d, *J* = 0.9); 5.94 (1H, s); 2.27 (3H, s).

5-Hydroxy-7-methyl-4-(3,4,5-trimethoxyphenyl)chromen-2-one (**3ee**). Brown crystals, mp 202-203ºC, R_f 0.43 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.16 (1H, br s); 6.70 (1H, d, *J* = 0.7); 6.64 (1H, s); 6.47 (1H, d, *J* = 0.7); 6.04 (1H, s); 3.75 (6H, s); 3.67 (3H, s); 2.28 (3H, s). Found, %: C 66.40; H 5.24; N 0.00. $C_{19}H_{18}O_6$. Calculated, %: C 66.66; H 5.30; N 0.00.

5-Hydroxy-7-methyl-4-(4-nitrophenyl)chromen-2-one (**3ef**). Yellow crystals, mp 292-293ºC (recrystallized from EtOH–H_2O) (lit. [32] decomp.>260ºC), R_f 0.39 (dichloromethane–methanol, 20:1). ^{1}H NMR, δ, ppm (*J*, Hz): 10.29 (1H, br s); 8.27-8.17 (2H, m); 7.67-7.56 (2H, m); 6.73 (1H, d, *J* = 1.0); 6.45 (1H, d, *J* = 1.0); 6.06 (1H, s); 2.28 (1H, s).

X-ray structure analysis of the compound 3ea-A. A single crystal diffractometer "Nonius KappaCCD" (Mo*K*α-radiation, λ = 0.71073 Å) was used for data collection. Colourless crystals of **3ea-A** are monoclinic, space group *C c*. Lattice parameters are *a* = 10.1290(6), *b* = 18.5051(8), *c* = 7.3777(4) Å, β = 132.147(2)°; *V* = 1025.29(9) Å^3, *Z* = 4, *F*(000) = 440, μ = 0.103 mm^{-1}, D_{calc} = 1.349 g/cm^3, $2\theta_{max}$ = 55.0°. A total of 3710 reflection intensities was collected at room temperature using φ and ω scan technique. The structure was solved using direct method [43]. For structure refinement, 2190 (R_{int} = 0.0364) independent reflections with $|F| > 4\sigma(F)$ was used. The structure refinement was carried out with the AREN complex of programs [44]. The final *R*-factor is 0.0543.

We thank Dr. S. Belyakov for X-ray crystallographic analysis and Dr. F. Fleisher for quantum-chemical calculations.

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