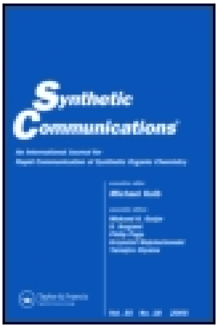

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Mechanically Activated Solid-State Synthesis of Flavones by High-Speed Ball Milling

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Mechanically Activated Solid-State Synthesis of Flavones by High-Speed Ball Milling

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Abstract: An efficient, mechanically activated solid-state synthesis of flavones from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones using high-speed ball milling is described. This method has notable advantages in terms of good yield, short reaction time, and neat conditions.

Keywords: Ball milling, flavones, solid-state synthesis

Flavones are a class of naturally occurring compounds with various biological activities.[1] One of the most commonly used methods for the synthesis of flavones is the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones. Many of these procedures use strong acids such as H_2SO_4,[2] HCl,[3] HBr, or HI[4] as the reagent or use $H_3PMo_{12}O_{40} \cdot nH_2O/SiO_2$,[5] nonaqueous cation-exchange resin,[6] or supported trifluoromethanesulfonic acid[7] as the catalyst. All of these require high temperatures or long times to complete the reactions. Other methods, including using Br_2 or I_2 under irradiation conditions[8] and using ionic liquid $[EtNH_3]NO_3$,[9] $CuCl_2$,[10] or montmorillonite K-10 clay[11] as the catalyst by microwave-assisted synthesis, have been reported with different yields.

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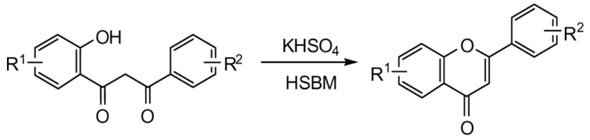


R_1 = H, Cl, Br, CH_3, OCH_3, NO_2, OH; R_2 = H, Cl, CH_3, OCH_3, NO_2

Scheme 1. Synthesis of flavones by high speed ball milling.

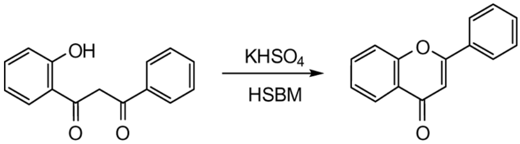
In recent years, solvent-free chemical synthesis has developed into a powerful methodology because it reduces the toxic waste produced and is less harmful to the environment. Mechanically activated solid-state reactions are solvent-free reactions conducted by grinding or ball milling. High-speed ball milling (HSBM) is an attractive, mechanically activated method that has started to gain attention. It is often used for milling minerals into fine particles and for the preparation and modification of inorganic solids.[12] In the field of synthetic organic chemistry, many applications also have been found, such as Heck-type cross-couplings,[13] asymmetric aldol reaction,[14] Baylis–Hillman reaction,[15] reduction of esters,[16] synthesis of fluoroaromatic compounds,[17] and protection of diamines, anthranilic acid, diols, and polyols.[18] However, the application of HSBM to the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones has not been reported.

It is known that $KHSO_4$ is an efficient reagent for different functional group transformations under heterogeneous conditions.[19] Because it is stable and inexpensive, together with its high efficiency in heterogeneous reaction, the reagent has received much attention in organic synthesis. Herein, we report the efficient synthesis of flavones by cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones in the presence of $KHSO_4$ by HSBM (Scheme 1).

RESULTS AND DISCUSSION

Our initial investigation focused on the cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione. To prevent "overheating" of the reaction mixture, a milling cycle with a rotational speed of 1290 rpm for 5 min followed by a 5-min pause was specified. This cycle could be repeated until the completion of the reaction. Different amounts of the catalyst were tested to seek the optimum conditions. As shown in Table 1, the best result with 94% yield was achieved when 20 mol% $KHSO_4$ was used as catalyst (Table 1, entry 3). Comparable yields could also be obtained by employing 50 mol% and

Table 1. Effect of $KHSO_4$ amount on the cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione under HSBM conditions[a]



Entry	$KHSO_4$ (mol%)	Time (min)	Yields (%)[b]
1	50	5	95
2	30	5	94
3	20	5	94
4	5	10	88
5	5	25	62

[a] Reactions were run with 10 mmol of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione, catalyst and 10 g silica gel.
[b] Isolated yield.

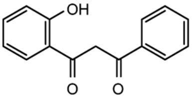
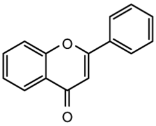
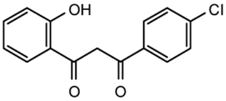
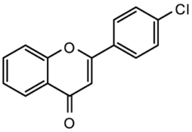
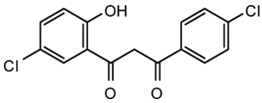
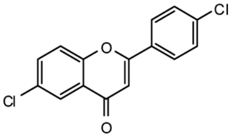
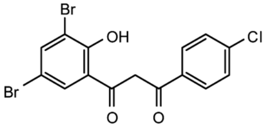
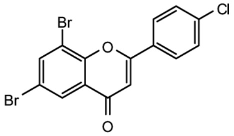
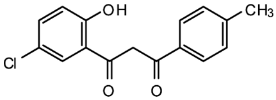
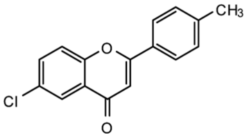
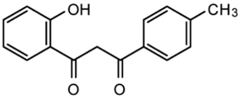
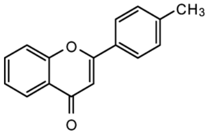
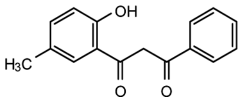
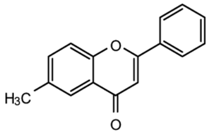
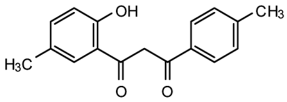
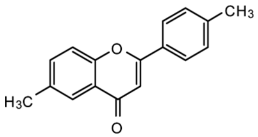
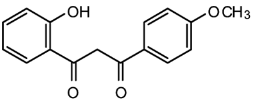
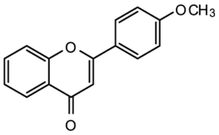
30 mol% $KHSO_4$ (Table 1, entries 1 and 2), but it is obvious that the use of an extra amount of catalyst was unnecessary. While using the lesser amounts of catalyst, longer reaction times and relatively poorer yields were observed in low catalyst loading (Table 1, entries 4 and 5).

In light of the good results obtained, several structurally diverse 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones were subjected to the optimized conditions for the preparation of flavones to explore the generality of the reaction. The results are listed in Table 2. It is worth noting that electron-withdrawing and electron-donating groups on the aromatic ring did not seem to affect the reaction significantly either in the yield of product or the rate of the reaction.

In a typical experiment, after the reaction was completed, $KHSO_4$ with silica gel was collected and dried at 120°C for 4 h to be regenerated. The reusability of the catalyst was examined with the 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione and resulted in 94, 92, 92, and 88% yields over four cycles (Table 3).

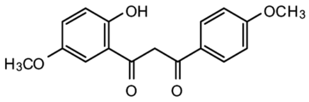
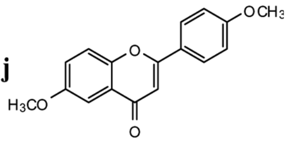
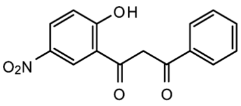
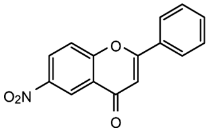
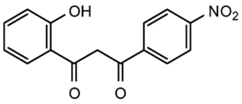
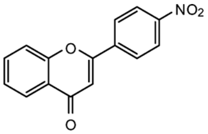
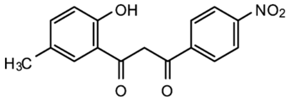
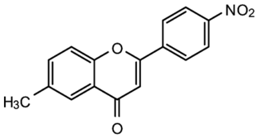
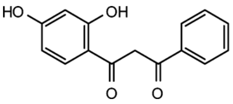
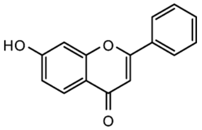
In conclusion, we have developed a novel and comparatively green strategy for the synthesis of flavones by HSBM. Good yields, short reaction times, and neat conditions are the notable advantages of this method. Catalyst recovery and reusability is another feature of this method. We believe that this procedure has provided a better scope for the synthesis of flavones. The application of HSBM to other synthetic reactions is now under investigation.

Table 2. Synthesis of flavones catalyzed by $KHSO_4$ under HSBM conditions[a]

Entry	Substrate		Product	Time (min)	Yields (%)[b]
1		**1a**		5	94
2		**1b**		5	93
3		**1c**		10	93
4		**1d**		15	90
5		**1e**		10	90
6		**1f**		5	94
7		**1g**		5	93
8		**1h**		5	91
9		**1i**		5	96

(*Continued*)

Table 2. Continued

Entry	Substrate		Product	Time (min)	Yields (%)[b]
10		**1j**		5	97
11		**1k**		15	88
12		**1l**		15	90
13		**1m**		15	89
14		**1n**		10	91

[a] Reactions were run with 10 mmol of substrate, 1 mmol of $KHSO_4$, and 10 g silica gel.

[b] Isolated yield.

Table 3. Reuse of $KHSO_4$ on the synthesis of flavone by HSBM[a]

Run	Time (min)	Yield of **1a** (%)[b]
1	5	94
2	5	92
3	5	92
4	10	88

[a] Reactions were run with 10 mmol of substrate, 1 mmol of $KHSO_4$, and 10 g silica gel.

[b] Isolated yield.

EXPERIMENTAL

1-(2-Hydroxyphenyl)-3-aryl-1,3-propanediones were prepared by procedures reported previously.[20] Other reagents were from commercial sources. The HSBM experiments were conducted in a planetary-centrifugal mill AGO-2 (acceleration: 60 g; volume of one drum: 35 ml; diameter of steel ball: 5 mm; weight of balls: 75 g). Melting points (mp) were recorded on a WRS-1B digital melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded in centimeters^{-1} on a Thermo Nicolet Avatar 370 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury Plus 400 spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard. Mass spectra (MS) were measured in m/z with a Finnigan Trace DSQ spectrometer. Elemental analyses were measured on a Thermo Finnigan Flash EA 1112 elemental analyzer.

Typical Procedure for Synthesis of Flavones

The following components were added to the reaction vessels: 1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione (10 mmol), $KHSO_4$ (0.27 g, 2 mmol), and silica gel (10 g, 200–300 mesh). Then, stainless steel balls were added, and the vessel was closed with lid and gasket. The ball mill was then run at a milling cycle with a rotational speed of 1290 rpm for 5 min followed by a 5-min pause. During the pause, a portion of the mixture was taken out and dissolved in CH_2Cl_2 to monitor the progress of the reaction using thin-layer chromatography (TLC). This cycle was repeated until the reaction was completed. The mixture was washed off the vessel using CH_2Cl_2 (20 ml) and then was filtered. The filtrate was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography to provide the corresponding product.

Data

2-Phenyl-4H-chromen-4-one (**1a**)

White solid: mp 96–97°C (lit.[21] 96–97°C). IR (KBr): 1646, 1605, 1568, 1128, 768. ^{1}H NMR (400 MHz, $CDCl_3$): 8.24 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.94 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.71 (*t*, $J = 8.0$ Hz, 1H, ArH), 7.53–7.60 (*m*, 4H, ArH), 7.43 (*t*, $J = 8.0$ Hz, 1H, ArH), 6.86 (*s*, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 163.33, 156.29, 133.77, 131.75, 131.59, 129.03, 126.27, 125.68, 125.21, 120.11, 118.17, 107.64. EI-MS: 222 (100, M^+), 194 (60), 165 (9), 120 (55), 92(43).

2-(4-Chlorophenyl)-4H-chromen-4-one (**1b**)

White solid: mp 185–187°C (lit.[22] 185–188°C). IR (KBr): 1641, 1466, 1090, 828, 772. ^{1}H NMR (400 MHz, $CDCl_3$): 8.21 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.84 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.70 (*t*, $J = 8.0$ Hz, 1H, ArH), 7.54 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.48 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.42 (*t*, $J = 8.0$ Hz, 1H, ArH), 6.78 (*s*, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 178.08, 162.09, 156.06, 137.79, 133.81, 130.15, 129.29, 127.47, 125.65, 125.27, 123.84, 117.95, 107.60. EI-MS: 258 (36, $M^+ + 2$), 256 (100, M^+), 230 (14), 228 (46), 221 (15), 120 (67), 92 (32).

6-Chloro-2-(4-chlorophenyl)-4H-chromen-4-one (**1c**)

White solid: mp 226–227°C (lit.[23] 226–227°C). IR (KBr): 1658, 1492, 1438, 1092, 906, 831, 664. ^{1}H NMR (400 MHz, $CDCl_3$): 8.19 (*s*, 1H, ArH), 7.85 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.64–7.67 (*m*, 1H, ArH), 7.51–7.54 (*m*, 3H, ArH), 6.79 (*s*, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 176.98, 162.51, 154.49, 138.21, 134.09, 131.40, 129.90, 129.47, 127.57, 125.25, 124.94, 119.75, 107.63. EI-MS: 290 (10, M^+), 293 (2, $M^+ + 2$), 262 (100), 199 (60), 163 (87).

6,8-Dibromo-2-(4-chlorophenyl)-4H-chromen-4-one (**1d**)

Yellow solid: mp 248–251°C (lit.[24] 249–250°C). IR (KBr): 1649, 1612, 1492, 1092, 839, 699. ^{1}H NMR (400 MHz, $CDCl_3$): 8.29 (*s*, 1H, ArH), 8.04 (*s*, 1H, ArH), 7.93 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.53 (*d*, $J = 8.0$ Hz, 2H, ArH), 6.84 (*s*, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 176.21, 162.51, 151.74, 139.47, 138.63, 129.63, 129.41, 127.89, 127.74, 126.00, 118.73, 118.11, 113.03, 107.29. EI-MS: 414 (100, M^+), 416 (74, $M^+ + 2$), 278 (98), 250 (11), 197 (16), 163 (10), 136 (15).

2-(4-Chlorophenyl)-7-methyl-4H-chromen-4-one (**1e**)

Yellow solid: mp 179–180°C. IR (KBr): 1638, 1490, 1410, 1092, 906, 827, 813. 477. ^{1}H NMR (400 MHz, $CDCl_3$): 8.05 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.77–7.80 (*m*, 2H, ArH), 7.43–7.46 (*m*, 2H, ArH), 7.29 (*s*, 1H, ArH), 7.19 (*d*, $J = 8.0$ Hz, 1H, ArH), 6.70 (*s*, 1H, ArH), 2.47 (*s*, 3H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): 177.89, 161.60, 156.05, 145.11, 137.55, 130.11, 129.14, 127.24, 126.66, 125.25, 121.46, 117.63, 107.36, 21.69. EI-MS: 270 (5, M^+), 242 (100), 178 (90), 152 (70), 78 (6). Anal. calc. for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.10. Found: C, 70.92; H, 4.04.

6-Chloro-2-p-tolyl-4H-chromen-4-one (**1e**)

Yellow solid: mp 183–184°C (lit.[24] 183–184°C). IR (KBr): 1641, 1613, 1465, 1436, 1358, 816, 670. ^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (*s*, 1H, ArH), 7.78 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.61 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.50 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.31 (*d*, $J = 8.0$ Hz, 2H, ArH), 6.79 (*s*, 1H, CH), 2.43 (*s*, 1H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 177.08, 163.79, 154.46, 142.55, 133.76, 131.02, 129,78, 128.45, 126.18, 125.07, 119.72, 106.75, 21.51. EI-MS: 270 (100, M^+), 272 (35), 255 (45), 242 (20), 154 (55), 116 (31), 115 (47).

2-p-Tolyl-4H-chromen-4-one (**1f**)

Yellow solid: mp 108–111°C (lit.[25] 108–111°C). IR (KBr): 1637, 1465, 1371, 1227, 817, 752, 634. ^{1}H NMR (400 MHz, $CDCl_3$): 8.21 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.78 (*s*, 2H, ArH), 7.65 (*t*, $J = 4.0$ Hz, 1H, ArH), 7.52 (*s*, 1H, ArH), 7.27 (*s*, 1H, ArH), 7.38 (*t*, $J = 8$ Hz, 2H, ArH), 6.76 (*s*, 1H, CH), 2.40 (*s*, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 178.26, 163.37, 156.05, 142.10, 133.49, 129.61, 128.73, 126.04, 125.49, 124.96, 123.83, 117.92, 106.76, 21.38. EI-MS: 236 (100, M^+), 221 (44), 120 (36), 115 (37), 104 (10), 92 (23).

6-Methyl-2-phenyl-4H-chromen-4-one (**1g**)

Yellow solid: mp 121–122°C (lit.[23] 122°C). IR (KBr): 1638, 1615, 1482, 1359, 1044, 883, 814, 778. ^{1}H NMR (400 MHz, $CDCl_3$): 8.00 (*s*, 1H, ArH), 7.90 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.43–7.52 (*m*, 5H, ArH), 6.79 (*s*, 1H, CH), 2.45 (*s*, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 178.46, 163.14, 154.43, 135.10, 134.90, 131.78, 131.42, 128.92, 126.16, 124.93, 123.51, 117,76, 107.31, 20.85. EI-MS: 236 (100, M^+), 208 (30), 134 (71), 106 (17), 78 (12).

6-Methyl-2-p-tolyl-4H-chromen-4-one (**1h**)

White solid: mp 151–152°C (lit.[23] 150–151°C). IR (KBr): 1643, 1613, 1483, 817. ^{1}H NMR (400 MHz, $CDCl_3$): 8.00 (*s*, 1H, ArH), 7.80

(*d*, $J = 8.0$ Hz, 2H, ArH), 7.44–7.50 (*m*, 2H, ArH), 7.31 (*d*, $J = 8.0$ Hz, 2H, ArH), 6.77 (*s*, 1H, CH), 2.46 (*s*, 3H, CH_3), 2.43 (*s*, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 178.49, 163.42, 154.50, 142.06, 135.03, 134.80, 129.70, 129.08, 126.16, 125.01, 123.64, 117.77, 106.81, 21.45, 20.88. EI-MS: 250 (100, M^+), 235 (30), 222 (25), 134 (80), 115 (17), 106 (17), 78 (10).

2-(4-Methoxyphenyl)-4H-chromen-4-one (**1i**)

White solid: mp 157–159°C (lit.[21] 157–158°C). IR (KBr): 1649, 1608, 1465, 1380, 1133, 827, 767. ^1H NMR (400 MHz, $CDCl_3$): 8.21 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.85 (*d*, $J = 8.4$ Hz, 2H, ArH), 7.65–7.69 (*m*, 1H, ArH), 7.53 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.40 (*t*, $J = 7.2$ Hz, 1H, ArH), 6.98–7.01 (*m*, 2H, ArH), 6.72 (*s*, 1H, CH), 3.87 (*s*, 1H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 178.22, 163.25, 162.28, 156.03, 133.45, 127.86, 125.50, 124.95, 123.80, 120.08, 117.86, 114.33, 106.01, 55.39. EI-MS: 252 (100, M^+), 237 (7), 221 (15), 209 (13), 132 (63).

6-Methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**1j**)

White solid: mp 196°C (lit.[26] 194–195°C). IR (KBr): 1649, 1608, 1515, 1466, 1382, 1268, 1195, 1026, 827, 768. ^1H NMR (400 MHz, $CDCl_3$): 7.88 (*d*, $J = 8.0$ Hz, 2H, ArH), 7.61 (*d*, $J = 4.0$ Hz, 1H, ArH), 7.45 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.29 (*d*, $J = 4.0$ Hz, 1H, ArH), 7.03 (*d*, $J = 8.0$ Hz, Hz, 2H, ArH), 6.76 (*s*, 1H, CH), 3.92 (*s*, 3H, OCH_3), 3.90 (*s*, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 178.30, 163.28, 162.36, 156.95, 151.04, 127.97, 124.54, 124.16, 123.59, 119.39, 114.47, 105.52, 104.91, 55.96, 55.51. EI-MS: 282 (100, M^+), 252 (22), 150 (98), 132 (23), 107 (28), 107 (28).

6-Nitro-2-phenyl-4H-chromen-4-one (**1k**)

Pale yellow solid: mp 194–195°C (lit.[27] 193°C). IR (KBr): 1646, 1610, 1454, 1340, 1135, 922, 841, 772, 679, 627. ^1H NMR (400 MHz, $CDCl_3$): 9.12 (*s*, 1H, ArH), 8.52 (*d*, $J = 8.0$ Hz, 1H, ArH), 7.93–7.95 (*m*, 2H, ArH), 7.74 (*d*, $J = 4.0$ Hz, 1H, ArH), 7.55–7.63 (*m*, 3H, ArH), 6.90 (*s*, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 176.67, 164.15, 159.08, 144.86, 132.39, 130.78, 129.30, 128.15, 126.45, 124.11, 122.52, 119.84, 107.89. EI-MS: 267 (100, M^+), 239 (17), 221 (22), 165 (32), 139 (18), 102 (61).

2-(4-Nitrophenyl)-4H-chromen-4-one (**1l**)

Pale yellow solid: mp 241–243°C (lit.[23] 242–244°C). IR (KBr): 1659, 1520, 1467, 1346, 1130, 857, 750, 692. ^{1}H NMR (400 MHz, $CDCl_3$): 8.11–8.40 (*m*, 5H, ArH), 7.48–7.76 (*m*, 3H, ArH), 6.92 (*s*, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 177.93, 160.56, 156.18, 149.46, 137.66, 134.31, 127.21, 125.88, 125.75, 124.23, 123.96, 118.19, 108.64. EI-MS: 267 (25, M^+), 236 (100), 208 (25), 166 (9), 115 (13), 92 (12).

6-Methy-2-(4-nitrophenyl)-4H-chromen-4-one (**1m**)

Yellow solid: mp 276–278°C (lit.[23] 275–277°C). IR (KBr): 1639, 1617, 1522, 1343, 1138, 850, 823, 691. ^{1}H NMR (400 MHz, $CDCl_3$): 8.39 (*d*, $J = 8.0$ Hz, 2H, ArH), 8.11 (*d*, $J = 8.0$ Hz, 2H, ArH), 8.03 (*s*, 1H, ArH), 7.50–7.58 (*m*, 2H, ArH), 6.90 (*s*, 1H, CH), 2.49 (*s*, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 178.16, 160.43, 154.52, 149.43, 137.82, 135.88, 135.56, 127.19, 125.27, 124.22, 123.73, 117.89, 109.53, 20.96. EI-MS: 281 (100, M^+), 253 (20), 134 (48), 106 (12).

7-Hydroxy-2-phenyl-4H-chromen-4-one (**1n**)

White solid: mp 240–242°C (lit.[28] 240°C). IR (KBr): 3118, 2593, 1626, 1552, 1512, 1454, 1384, 1166. ^{1}H NMR (400 MHz, $CDCl_3$): 10.84 (*s*, 1H, OH), 8.06–8.08 (*m*, 2H, ArH), 7.90 (*d*, $J = 6.8$ Hz, 1H, ArH), 7.56–7.60 (*m*, 3H, ArH), 7.02 (d, $J = 2.0$ Hz, 1H, ArH), 6.94 (*dd*, $J = 2.0$ Hz, 7.0 Hz, 1H, ArH), 6.91 (*s*, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 176.33, 162.74, 161.91, 157.48, 131.48, 131.29, 129.03, 126.50, 126.13, 116.15, 115.04, 106.62, 102.52. EI-MS: 238 (100, M^+), 237 (22), 210 (82), 136 (21), 108 (24).

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