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A Simple Synthesis of Functionalized 3-Bromocoumarins by a One-Pot Three-Component Reaction

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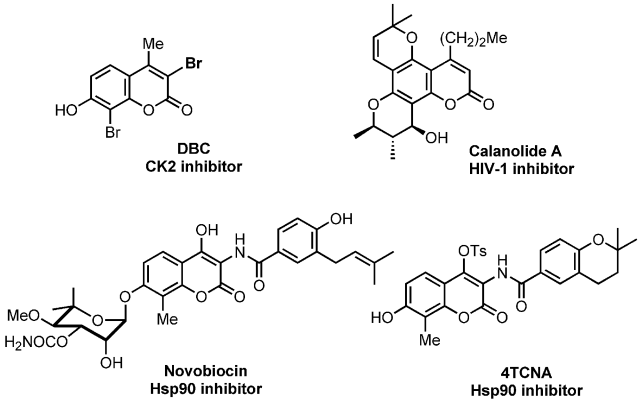
Functionalized 3-bromocoumarins **2** have been prepared by a simple one-pot bromination/Wittig/cyclization tandem process from methyl (triphenylphosphoranylidene)acetate, *N*-bromosuccinimide and a series of 2-hydroxybenzaldehydes. Owing to the commercial availability of salicylaldehyde derivatives, this approach offers such a diverse range of compounds that it fulfills the recent demand for the generation of large combinatorial chemical libraries based on the coumarin scaffold.

Introduction

Coumarins (2*H*-chromen-2-ones) are among the best-known oxygen heterocycles and are present as a structural motif in numerous natural products. Since the first isolation of coumarin in 1820, over 1400 natural coumarins have been isolated.[1] The coumarin ring system is a useful structure in heterocyclic synthesis and it displays a variety of important biological activities, including anti-coagulation, antibiotic,[2] anti-psoriasis, anti-HIV[3] and anti-tumour activities.[4] 3,8-Dibromo-7-hydroxy-4-methylchromen-2-one (DBC),[5] the most promising inhibitor of Casein kinase 2 (CK2), and calanolide A,[6] which inhibits HIV-1 replication, are examples of bioactive substituted 2*H*-chromen-2-ones. Novobiocin[7] and its denoviose analogue 4TCNA,[8] two 3-amidocoumarin derivatives (Scheme 1), have been shown to bind to the C-terminal domain of heat-shock protein 90 (hsp90), an exciting new target in cancer drug discovery[9] that leads to a decrease in hsp90 client proteins in various cancer cell lines.[8,10]

In an ongoing medicinal chemistry program directed towards the synthesis of novobiocin analogues,[8,10] we recently reported a convenient protocol for the rapid synthesis of 3-(*N*-substituted) amidocoumarins[11,12] based on the palladium-catalysed C–N coupling reaction between nitrogen nucleophiles and 3-bromocoumarins. The latter are of particular interest because the coupling reaction offers a convergent and straightforward approach to various 3-(*N*-substituted) aminocoumarins. In an effort to identify more potent hsp90 inhibitors, we became interested in the synthesis of a combinatorial library based on the scaffold of 3-aminocoumarin **1** (Scheme 2). To this end, we required a simple and versatile access to a variety of functionalized 3-bromocoumarins of type **2**. A survey of the literature revealed that few methods for their preparation have been developed. The most common is undoubtedly the classic treatment of the coumarin nucleus with an electrophilic bromine source.[13] Although this method has been utilized successfully with unsubstituted coumarins, the protocol suffers from several limitations, the most important being the difficulty of selective C-3 bromination of the coumarin heterocycle bearing electron-donating substituents at C-6 and/or C-7, which give a complex mixture of halogenated products[14] or exclusive bromination of the aromatic nucleus.[15] Because the existing routes to **2** are either inappropriate or unattractive due to the complicated synthetic procedure we became interested in developing an alternative and simple method for its synthesis.



Scheme 1. Chemical structures of some bioactive substituted coumarins.

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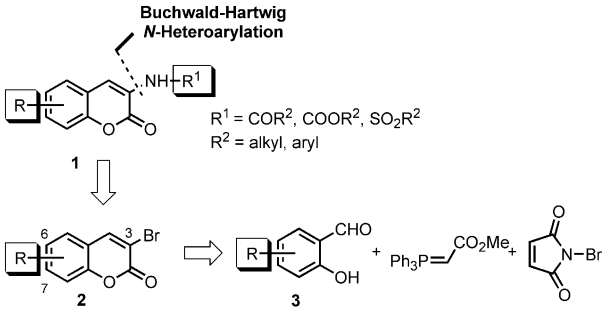


Scheme 2. Target 3-bromocoumarin derivatives **2** and the three-component synthetic strategy envisaged for its synthesis.

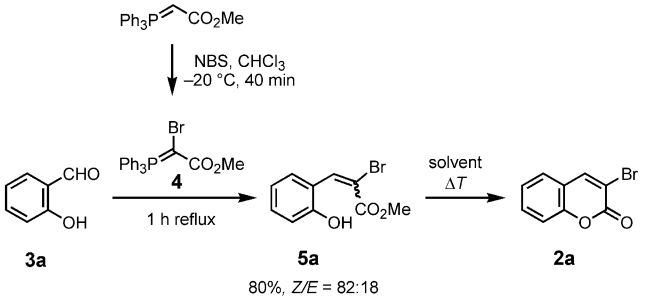
Our strategy focused on the use of a one-pot three-component reaction between readily available substituted salicylaldehydes **3**, methyl (triphenylphosphoranylidene)acetate and *N*-bromosuccinimide (NBS). We envisaged that bromination of phosphorane would first take place followed by a rapid Wittig reaction leading to C=C double bond formation. Subsequent intramolecular cyclization would furnish the desired 3-bromocoumarin derivatives **2** (Scheme 2). This procedure offers a selective and straightforward approach to various 3-bromocoumarins. We report the results of this study herein.

Results and Discussion

Our first attempt to prepare the target compounds **2** began with the use of salicylaldehyde (**3a**) as a model substrate. We decided to perform the transformation in a sequential way by mixing the preformed ylide **4**[16] with **3a** to obtain the intermediate **5a** and then to heat this compound to give **2a**. However, the reaction of salicylaldehyde (**3a**) with **4** in $CHCl_3$ at room temperature failed and only the starting material was recovered. Raising the temperature to 62 °C produced within 1 h bromocinnamate intermediate **5a** in 80% isolated yield as a mixture of *Z*/*E* isomers (82:18).[17] With the improvement in this first step, we screened the conditions for the selective intramolecular cyclization reaction of **5a** (Table 1).

As summarized in Table 1, the yield of 3-bromocoumarin (**2a**) increased when the reaction temperature was raised. Thus, running the reaction in toluene at 110 °C for 14 h did not promote any cyclization (entry 1) and **5a** was recovered unchanged. When the reaction was conducted in mesitylene at 165 °C, we observed complete conversion of **5a** after only 7 h and the expected product **2a** was formed in a satisfactory 60% yield from an isomerization/cyclization process (entry 2). A similar result was obtained on heating the medium for a longer reaction time (entry 3). However, carrying out the reaction in a sealed Schlenk tube under pressure at 200 °C also led to the total conversion of **5a**, but after only 2 h, and gave **2a** in a slightly better yield (70%, entry 4). Finally, the best result was obtained by heating the medium in diphenyl ether (DPE) as solvent at 200 °C for 1 h. Under

Table 1. Optimization of the cyclization reaction of **5a** under various conditions.



Entry	Solvent	*T* [°C]	Time [h]	% Yield[a]
1	toluene	110	14	–
2	mesitylene	165	7	60
3	mesitylene	165	14	61
4	mesitylene	200[b]	2	70
5	DPE[c]	200	1	82[d]

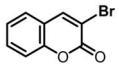
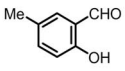
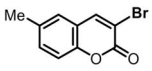
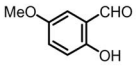
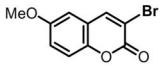
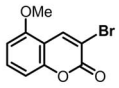
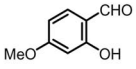
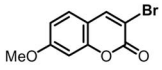
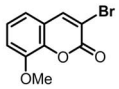
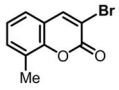
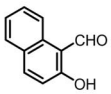
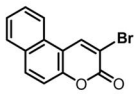
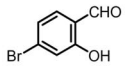
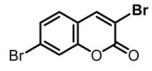
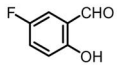
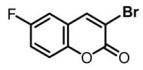
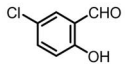
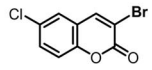
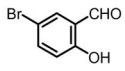
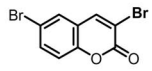
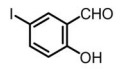
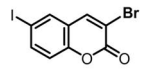
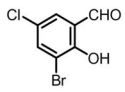
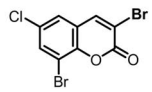
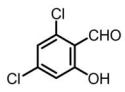
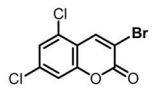
[a] Isolated yield. [b] Performed in a sealed Schlenk tube. [c] DPE: diphenyl ether. [d] The reaction was repeated three times and a reproducible yield was obtained.

these conditions, the intramolecular cyclization reaction proved to be effective, providing **2a** in 82% isolated yield (entry 5).

To obviate the direct manipulation and purification of intermediate **5a**, we next examined a one-pot bromination/Wittig/cyclization sequence as it would be economically and environmentally advantageous for a multistep synthesis. In this context, mixing methyl (triphenylphosphoranylidene)-acetate and NBS in chloroform promoted the bromination reaction. The chloroform was removed under reduced pressure and then salicylaldehyde and DPE were introduced successively and the reaction medium was heated at 80 °C for 1 h and then at 200 °C for 2 h. Under this protocol we observed that the reaction worked well and provided the desired 3-bromocoumarin (**2a**) in 71% yield.

To generate a small library of functionalized 3-bromocoumarins **2**, we next utilized a variety of salicylaldehydes **3** to explore the scope of this accelerated one-pot bromination/Wittig/cyclization cascade reaction under the optimal conditions. Representative results are shown in Table 2. Overall, the method works well and tolerates a large variety of electron-rich and -deficient groups on the aromatic ring of the salicylaldehyde.[18] Substrates with electron-donating groups at C-3 or C-5 of the aromatic nucleus of salicylaldehyde, such as **3b**, **3c**, **3f** or **3g**, led to the formation of the corresponding 3-bromocoumarins **2b**, **2c**, **2f** and **2g**, respectively, in 62–86% yields (entries 2, 3, 6 and 7). Moving the electron-donating group to C-4 or C-6, however, resulted in lower reaction yields (entries 4 and 5), with the lowest yield being obtained with 2-hydroxy-5-methoxybenzaldehyde (**3e**; 24%, entry 5). This result clearly indicates that the position of the substituent borne by the aromatic ring influences the progress of the reaction. Interestingly, this method is also

Table 2. Synthesis of functionalized 3-bromocoumarins **2** by a one-pot bromination/Wittig/cyclization sequence.[a]

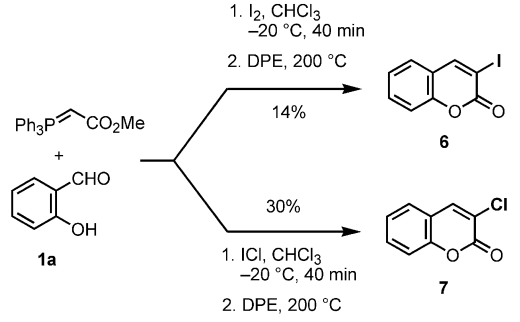
Entry	Salicylaldehyde **3**		Product **2**		Yield (%)[b]
1		**3a**		**2a**	71
2		**3b**		**2b**	86
3		**3c**		**2c**	67[c]
4		**3d**		**2d**	49[d]
5		**3e**		**2e**	24[e]
6		**3f**		**2f**	69
7		**3g**		**2g**	62
8		**3h**		**2h**	54
9		**3i**		**2i**	60
10		**3j**		**2j**	76
11		**3k**		**2k**	62
12		**3l**		**2l**	72[f]
13		**3m**		**2m**	27 (73)[g]
14		**3n**		**2n**	64
15		**3o**		**2o**	70

[a] For the general procedure, see the Exp. Sect. [b] Isolated yield. [c] The classic treatment of 6-methoxycoumarin with Br_2 in acetic acid led to exclusive bromination at C-5 of the aromatic nucleus.[20] [d] The classic treatment of 5-methoxycoumarin with Br_2 in acetic acid led to exclusive bromination at C-8 of the aromatic nucleus.[21] [e] A 25% yield of 7-methoxycoumarin was isolated as a side-product. [f] No reaction occurred when 6-bromocoumarin was treated with Br_2 in AcOH at 80 °C, only the starting material was recovered unchanged. [g] The overall yield given in parentheses refers to a stepwise reaction between **4** and **3m** followed by cyclization of the isolated intermediate **5m**.

quite effective with substrate **3h** and was used to synthesize tricyclic compound 3-bromobenzocoumarin **2h** in satisfactory yield (entry 8).

The scope of the reaction was further examined by applying the optimized conditions to various halogenated salicylaldehydes **3i**–**o**. It was found that halogen atoms at C-4 or C-5 were also tolerated, yielding dihalogenated coumarins **2i**–**m** which may be useful for regioselective cross-coupling reactions (entries 9–13). Note that under the optimal conditions, the dihalogenated coumarin **2m** was prepared in only 27% yield, even after prolonged stirring. To improve this result, we decided to perform this transformation in a stepwise manner by mixing **3m** with preformed ylide **4** in a first step to isolate the intermediate **5m** and then by heating this in DPE in a second step. Under this stepwise protocol we observed that the tandem sequence worked well and provided the desired 3-bromo-6-iodocoumarin (**2m**) in 73% yield. More interestingly, trihalogenated coumarin derivatives **2n** and **2o**, which have hitherto not been reported, were also prepared in satisfactory yields by using this one-pot protocol (64 and 70% respectively, entries 14 and 15).

Having developed this novel procedure for the synthesis of functionalized 3-bromocoumarins **2**, we sought to extend the methodology to the preparation of 3-chloro- and 3-iodocoumarin derivatives by using other sources of electrophiles. Thus, by mixing methyl (triphenylphosphoranylidene)acetate with *N*-iodosuccinimide in $CHCl_3$ and then adding **1a**, unexpectedly, no reaction occurred, whereas in the presence of molecular iodine the expected 3-iodocoumarin (**6**) was formed, but in a low yield (14%, Scheme 3). Switching to ICl, we were pleased to observe that the reaction proceeded smoothly and provided the 3-chlorinated coumarin **7** in a moderate 30% yield, despite the fact that the reaction conditions have not been optimized (Scheme 3). Under these conditions, iodine monochloride acts, as described previously,[19] as a source of "Cl^+". Further studies of the optimization and scope of this transformation are underway.



Scheme 3. Preliminary results on the synthesis of 3-iodo- and 3-chlorocoumarins (**6** and **7**).

Conclusions

We have successfully developed a highly efficient and general method for the synthesis of functionalized 3-halocoumarins by an accelerated one-pot bromination/Wittig/cycli-

zation reaction. A number of functional groups, such as fluoro, chloro, bromo, iodo and methoxy, are tolerated under the reaction conditions to provide structurally interesting halogenated coumarins in satisfactory-to-good yields. Given the range of commercially available components for this protocol (salicylaldehydes), the method should prove valuable in the preparation of combinatorial libraries of functionalized coumarins. Further studies to extend the scope of this reaction to diverse nitrogen and sulfur heterocyclic compounds are in progress in our laboratory. The synthesis of a small library of functionalized 3-aminocoumarins related to novobiocin as potential Hsp90 inhibitors will be reported in due course.

Experimental Section

General Procedure for the One-Pot Synthesis of 3-Bromocoumarins: Freshly crystallized *N*-bromosuccinimide[22] (1.8 mmol, 315.0 mg) was added portionwise under argon to a solution of methyl (triphenylphosphoranylidene)acetate (1.6 mmol, 538.0 mg) in dry chloroform (5 mL) cooled to –20 °C. The solution was stirred for 40 min at –20 °C and then the solvent was evaporated under reduced pressure in a water bath at room temperature. Diphenyl ether (5 mL) and salicylaldehyde (1.35 mmol) were then added successively. After stirring for 1 h at 80 °C, the solution was heated at 200 °C for 2 h. The mixture was cooled to room temperature and the residue purified by silica gel column chromatography using cyclohexane (to remove DPE) and then cyclohexane/EtOAc (8:2) as eluents.

Compound 5a: Mixture of *Z*/*E* isomers (82:18). *Z* isomer: Yield 70% (204 mg); yellow solid, m.p. 140–142 °C. TLC: R_f = 0.35 (*c*-hexane/AcOEt, 7:3). IR (neat): $\tilde{\nu}$ = 3345, 2953, 1689, 1603, 1489, 1453, 1437, 1411, 1352, 1301, 1248, 1191, 1158, 1101, 1042, 944, 910, 819, 756, 640, 618 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (s, 1 H), 8.01 (d, J = 7.9 Hz, 1 H), 7.29 (t, J = 8.5 Hz, 1 H), 6.99 (t, J = 7.6 Hz, 1 H), 6.86 (dd, J_1 = 8.1, J_2 = 0.9 Hz, 1 H), 5.71 (br. s, 1 H, OH), 3.91 (s, 3 H, CO_2Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 154.3, 136.6, 131.6, 129.7, 121.2, 120.4, 115.8, 113.5, 53.7 ppm. MS (APCI+): m/z = 257.0 [M + Na]$^+$ (^{79}Br), 259.0 [M + Na]$^+$ (^{81}Br). $C_{10}H_9BrO_3$ (255.97): calcd. C 46.72, H 3.53; found C 46.81, H 3.62.

Compound 2a:[23] Yield 71% (216 mg); white solid, m.p. 108–110 °C. TLC: R_f = 0.66 (CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3052, 1727, 1713, 1604, 1559, 1482, 1443, 1353, 1329, 1275, 1245, 1214, 1159, 1140, 1120, 1026, 955, 933, 915, 809, 762, 750, 726 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.55 (ddd, J_1 = 8.5, J_2 = 7.3, J_3 = 1.5 Hz, 1 H), 7.45 (dd, J_1 = 7.9, J_2 = 1.1 Hz, 1 H), 7.32–7.27 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 153.1, 144.3, 132.0, 127.1, 124.9, 119.2, 116.7, 111.7 ppm. MS (ESI+): m/z = 247.0 [M + Na]$^+$ (^{79}Br), 249.0 [M + Na]$^+$ (^{81}Br). $C_9H_5BrO_2$ (223.95): calcd. C 48.03, H 2.24; found C 48.14, H 2.36.

Compound 2b: Yield 86% (304 mg); white solid, m.p. 133–135 °C. TLC: R_f = 0.50 (*c*-hexane/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 1725, 1607, 1564, 1484, 1341, 1275, 1258, 1147, 964, 872, 828, 813, 751, 686, 620 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.32 (dd, J_1 = 8.5, J_2 = 2.0 Hz, 1 H), 7.18 (s, 1 H), 7.15 (d, J = 8.5 Hz, 1 H), 2.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 151.1, 144.2, 134.7, 133.0, 126.7, 118.8, 116.2, 111.4, 20.6 ppm. MS (APCI+): m/z = 239.0 [M + H]$^+$ (^{79}Br), 241.0 [M + H]$^+$ (^{81}Br). $C_{10}H_7BrO_2$ (237.96): calcd. C 50.24, H 2.95; found C 50.31, H 2.98.

Compound 2c: Yield 67% (226 mg); yellow solid, m.p. 163–165 °C. TLC: R_f = 0. 31 (*c*-hexane/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 1718, 1611, 1563, 1489, 1466, 1429, 1277, 1153, 1036, 971, 948, 867, 815, 746, 692, 616 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.24 (d, J = 9.1 Hz, 1 H), 7.11 (dd, J_1 = 9.1, J_2 = 2.9 Hz, 1 H), 6.85 (d, J = 2.9 Hz, 1 H), 3.83 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1, 156.4, 147.6, 144.1, 119.7, 119.6, 117.7, 112.4, 109.1, 55.8 ppm. MS (APCI+): m/z = 255.0 [M + H]$^+$ (^{79}Br), 257.0 [M + H]$^+$ (^{81}Br). $C_{10}H_7BrO_3$ (253.96): calcd. C 47.24, H 2.77; found C 47.29, H 2.98.

Compound 2d: Yield 49% (157 mg); white solid, m.p. 170–172 °C. TLC: R_f = 0. 40 (*c*-hexane/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 1729, 1603, 1474, 1439, 1347, 1285, 1249, 1224, 1129, 1090, 959, 928, 779, 724, 617 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 7.44 (t, J = 8.4 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 6.71 (d, J = 8.3 Hz, 1 H), 3.92 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 155.2, 154.0, 139.7, 132.6, 110.0, 109.4, 108.8, 105.5, 56.1 ppm. MS (APCI+): m/z = 255.0 [M + H]$^+$ (^{79}Br), 257.0 [M + H]$^+$ (^{81}Br). $C_{10}H_7BrO_3$ (253.96): calcd. C 47.24, H 2.77; found C 47.33, H 2.81.

Compound 2e: Yield 24% (120 mg); white solid, m.p. 158–160 °C. TLC: R_f = 0.65 (*c*-hexane/AcOEt, 7:3). IR (neat): $\tilde{\nu}$ = 1720, 1599, 1504, 1457, 1438, 1355, 1280, 1221, 1194, 1164, 1126, 1016, 989, 938, 826, 748, 720, 636, 615 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.34 (d, J = 8.6 Hz, 1 H), 6.86 (dd, J_1 = 8.7, J_2 = 1.4 Hz, 1 H), 6.80 (s, 1 H), 3.87 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 157.4, 155.0, 144.4, 128.1, 113.2, 113.0, 107.7, 100.7, 55.8 ppm. MS (APCI+): m/z = 255.0 [M + H]$^+$ (^{79}Br), 257.0 [M + H]$^+$ (^{81}Br). $C_{10}H_7BrO_3$ (253.96): calcd. C 47.24, H 2.77; found C 47.39, H 2.87.

Compound 2f: Yield 69% (175 mg); white solid, m.p. 147–149 °C. TLC: R_f = 0. 20 (*c*-hexane/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 1715, 1602, 1566, 1471, 1437, 1350, 1271, 1250, 1175, 1097, 943, 920, 868, 781, 745, 723, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.20 (t, J = 8.0 Hz, 1 H), 7.07 (d, J = 8.2 Hz, 1 H), 6.98 (d, J = 7.8 Hz, 1 H), 3.92 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 147.0, 144.5, 142.6, 124.9, 119.8, 118.3, 113.8, 112.0, 56.2 ppm. MS (APCI+): m/z = 255.0 [M + H]$^+$ (^{79}Br), 257.0 [M + H]$^+$ (^{81}Br). $C_{10}H_7BrO_3$ (253.96): calcd. C 47.24, H 2.77; found C 47.29, H 2.90.

Compound 2g: Yield 62% (216 mg); white solid, m.p. 127–129 °C. TLC: R_f = 0. 28 (*c*-hexane/AcOEt, 9:1). IR (neat): $\tilde{\nu}$ = 1713, 1599, 1567, 1456, 1380, 1349, 1250, 1168, 1135, 1083, 1063, 983, 952, 922, 901, 875, 783, 769, 748, 679 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.44 (d, J = 7.2 Hz, 1 H), 7.32 (d, J = 6.6 Hz, 1 H), 7.24 (t, J = 7.5 Hz, 1 H), 2.47 (s, 1 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 151.4, 144.6, 133.3, 126.2, 124.8, 124.5, 118.9, 111.2, 15.2 ppm. MS (APCI+): m/z = 239.0 [M + H]$^+$ (^{79}Br), 241.0 [M + H]$^+$ (^{81}Br). $C_{10}H_7BrO_2$ (237.96): calcd. C 50.24, H 2.95; found C 50.39, H 3.01.

Compound 2h: Yield 54% (171 mg); beige solid, m.p. 169–171 °C. TLC: R_f = 0. 50 (*c*-hexane/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 3053, 1730, 1626, 1585, 1556, 1511, 1434, 1327, 1277, 1211, 1131, 971, 915, 822, 775, 749, 727, 692, 673, 613 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73 (s, 1 H), 8.10 (d, J = 8.4 Hz, 1 H), 7.97 (d, J = 9.1 Hz, 1 H), 7.89 (d, J = 8.1 Hz, 1 H), 7.68 (t, J = 6.9 Hz, 1 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.38 (dd, J_1 = 9.0, J_2 = 0.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1, 152.9, 140.3, 133.3, 130.2, 129.0, 128.5, 127.9, 126.4, 121.2, 116.5, 113.4, 111.1 ppm. MS (APCI+): m/z = 275.0 [M + H]$^+$ (^{79}Br), 277.0 [M + H]$^+$ (^{81}Br). $C_{13}H_7BrO_2$ (273.96): calcd. C 56.76, H 2.56; found C 56.87, H 2.69.

Compound 2i: Yield 60% (182 mg); white solid, m.p. 181–183 °C. TLC: R_f = 0. 46 (*c*-hexane/AcOEt, 9:1). IR (neat): $\tilde{\nu}$ = 1729, 1687, 1596, 1481, 1396, 1343, 1243, 1198, 1144, 1124, 1065, 964, 912, 863, 809, 747, 718, 683, 651, 613 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.52 (d, J = 1.6 Hz, 1 H), 7.44 (dd, J_1 = 8.3, J_2 = 1.6 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 153.3, 146.6, 128.4, 127.9, 125.9, 120.1, 118.2, 112.1 ppm. MS (APCI+): m/z = 303.0 $[M + H]^+$ (^{79}Br), 305.0 $[M + H]^+$ (^{81}Br), 307.0 $[M + H]^+$ ($2 \times ^{81}Br$). $C_9H_4Br_2O_2$ (301.86): calcd. C 35.57, H 1.33; found C 35.92, H 1.52.

Compound 2j: Yield 76% (264 mg); white solid, m.p. 160–162 °C (lit.: 160–162 °C).[24] TLC: R_f = 0. 39 (*c*-hexane/AcOEt, 9:1). IR (neat): $\tilde{\nu}$ = 3051, 1730, 1562, 1483, 1427, 1333, 1256, 1135, 964, 934, 876, 822, 747, 689, 622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.36–7.25 (m, 2 H), 7.17 (dd, J_1 = 7.7, J_2 = 2.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9 (d, $J_{C,F}$ = 245.6 Hz, 1 C), 156.6, 149.3, 143.3 (d, $J_{C,F}$ = 2.4 Hz, 1 C),119.9 (d, $J_{C,F}$ = 9.3 Hz, 1 C), 119.5 (d, $J_{C,F}$ = 24.6 Hz, 1 C), 118.4 (d, $J_{C,F}$ = 8.5 Hz, 1 C), 113.5, 112.4 (d, $J_{C,F}$ = 24.4 Hz, 1 C) ppm. MS (APCI+): m/z = 243.0 $[M + H]^+$ (^{79}Br), 245.0 $[M + H]^+$ (^{81}Br). $C_9H_4BrFO_2$ (241.94): calcd. C 44.48, H 1.66; found C 44.62, H 1.72.

Compound 2k: Yield 62% (208 mg); white solid, m.p. 172–174 °C. TLC: R_f = 0. 25 (*c*-hexane/AcOEt, 95:5). IR (neat): $\tilde{\nu}$ = 1719, 1600, 1556, 1475, 1407, 1264, 1238, 1178, 1130, 1078, 924, 818, 751, 649, 607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.51 (dd, J_1 = 8.8, J_2 = 2.4 Hz, 1 H), 7.44 (d, J = 2.4 Hz, 1 H), 7.29 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 151.5, 143.0, 132.0, 130.3, 126.2, 120.2, 118.2, 113.4 ppm. MS (APCI+): m/z = 259.0 $[M + H]^+$ (^{79}Br), 261.0 $[M + H]^+$ (^{37}Cl), 263.0 $[M + H]^+$ (^{37}Cl, ^{81}Br). $C_9H_4BrClO_2$ (257.91): calcd. C 41.66, H 1.55; found C 41.84, H 1.78.

Compound 2l: Yield 72% (219 mg); white solid, m.p. 185–187 °C (lit.: 180–183 °C).[25] TLC: R_f = 0. 33 (*c*-hexane/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 1721, 1597, 1551, 1470, 1402, 1330, 1264, 1234, 1138, 1065, 962, 924, 840, 816, 751, 638 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.65 (dd, J_1 = 8.8, J_2 = 2.3 Hz, 1 H), 7.60 (d, J = 2.2 Hz, 1 H), 7.24 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 152.0, 142.9, 134.8, 129.3, 120.7, 118.5, 117.6, 113.4 ppm. MS (APCI+): m/z = 303.0 $[M + H]^+$ (^{79}Br), 305.0 $[M + H]^+$ (^{81}Br), 307.0 $[M + H]^+$ ($2 \times ^{81}Br$). $C_9H_4Br_2O_2$ (301.86): calcd. C 35.57, H 1.33; found C 35.86, H 1.61.

Compound 2m: Yield 27% (75 mg); yellow solid, m.p. 153–155 °C. TLC: R_f = 0. 30 (*c*-hexane/AcOEt, 95:5). IR (neat): $\tilde{\nu}$ = 1726, 1592, 1547, 1468, 1396, 1330, 1266, 1133, 964, 922, 831, 812, 750, 632 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.78 (dd, J_1 = 8.7, J_2 = 2.0 Hz, 1 H), 7.77 (d, J = 1.6 Hz, 1 H), 7.10 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 152.7, 142.8, 140.5, 135.3, 121.2, 118.7, 113.1, 87.8 ppm. MS (APCI+): m/z = 350.9 $[M + H]^+$ (^{79}Br), 352.9 $[M + H]^+$ (^{81}Br). $C_9H_4BrIO_2$ (349.84): calcd. C 30.80, H 1.15; found C 30.93, H 1.31.

Compound 2n: Yield 64% (184 mg); white solid, m.p. 175–177 °C. TLC: R_f = 0. 60 (*c*-hexane/AcOEt, 8:2). IR (neat): $\tilde{\nu}$ = 1736, 1543, 1409, 1333, 1239, 1219, 1143, 1097, 979, 925, 865, 808, 748, 679, 609 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.75 (d, J = 2.3 Hz, 1 H), 7.40 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 148.6, 142.6, 134.9, 130.5, 125.5, 120.8, 114.2, 111.1 ppm. MS (APCI+): m/z = 337.0 $[M + H]^+$, 339.0 $[M + H]^+$ (^{37}Cl), 341.0 $[M + H]^+$ (^{37}Cl, ^{81}Br), 343.0 $[M + H]^+$ (^{37}Cl, $2 \times ^{81}Br$). $C_9H_3Br_2ClO_2$ (335.82): calcd. C 31.95, H 0.89; found C 32.03, H 1.01.

Compound 2o: Yield 70% (216 mg); white solid, m.p. 146–148 °C. TLC: R_f = 0. 42 (*c*-hexane/AcOEt, 95:5). IR (neat): $\tilde{\nu}$ = 3077, 1749, 1595, 1392, 1335, 1313, 1222, 1196, 1125, 1086, 989, 950, 909, 884, 853, 748, 721, 633 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.39 (d, J = 0.5 Hz, 1 H), 7.37 (d, J = 1.9 Hz, 1 H), 7.27 (dd, J_1 = 0.5, J_2 = 1.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 153.8, 140.1, 137.8, 132.0, 125.9, 116.6, 116.1, 113.1 ppm. MS (APCI+): m/z = 293.0 $[M + H]^+$ (^{79}Br), 295.0 $[M + H]^+$ (^{81}Br), 297.0 $[M + H]^+$ ($2 \times ^{37}Cl$]. $C_9H_3BrCl_2O_2$ (291.87): calcd. C 36.78, H 1.03; found C 36.89, H 1.11.

Compound 6: Yield 14% (71 mg). The spectroscopic data are in agreement with those published in the literature.[26]

Compound 7: Yield 30% (51 mg). The spectroscopic data are in agreement with those published in the literature.[27]

Supporting Information (see also the footnote on the first page of this article): NMR spectra of all new compounds.

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[17] The *Z*/*E* ratio was determined by ^{1}H NMR spectroscopy on the basis of the chemical shifts of vinyl protons of the crude mixtures.
[18] In most cases small amounts of the corresponding dehalogenated coumarins (<10%) were observed as side-products. Nevertheless, these products were separated with ease by column chromatography.
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[20] 5-Bromo-6-methoxycoumarin: Yield 72%; yellow solid. TLC: R_f = 0.16 (*c*-hexane/CH_2Cl_2, 5:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 10.0 Hz, 1 H), 7.21 (d, J = 9.5 Hz, 1 H), 7.05 (d, J = 9.5 Hz, 1 H), 6.42 (d, J = 10.0 Hz, 1 H), 3.87 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 152.9, 148.7, 142.2, 119.6, 118.1, 116.3, 115.3, 110.7, 57.0 ppm. MS (APCI+): m/z = 255.0 $[M + H]^+$ (^{79}Br), 257.0 $[M + H]^+$ (^{81}Br).
[21] 8-Bromo-5-methoxycoumarin: Yield 69%; yellow solid. TLC: R_f = 0.6 (*c*-hexane/CH_2Cl_2, 5:5). ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 8.00 (d, J = 9.5 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 1 H), 6.85 (d, J = 8.0 Hz, 1 H), 6.38 (d, J = 9.0 Hz, 1 H), 3.87 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 159.2, 155.4, 150.6, 138.6, 135.5, 115.2, 110.4, 107.8, 99.6, 56.7 ppm. MS (APCI+): m/z = 255.0 $[M + H]^+$ (^{79}Br), 257.0 $[M + H]^+$ (^{81}Br).
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