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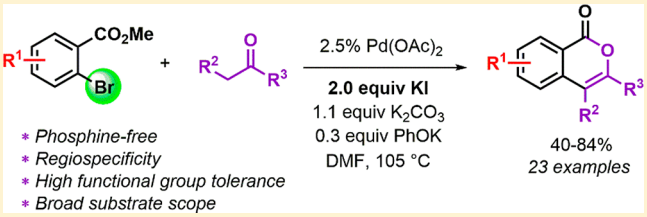
Pd-Catalyzed/Iodide-Promoted α-Arylation of Ketones for the Regioselective Synthesis of Isocoumarins

Alessandra Casnati, Raimondo Maggi, Giovanni Maestri, Nicola Della Ca',* and Elena Motti*

Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale (SCVSA), Università di Parma, Parco Area delle Scienze, 17/A, 43124 Parma, Italy

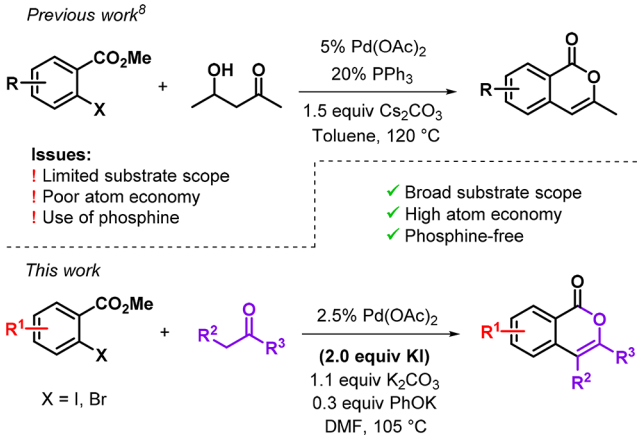
Supporting Information

ABSTRACT: A variety of isocoumarins have been synthesized directly from 2-halobenzoates and ketones through a palladium-catalyzed α-arylation step followed by an intramolecular cyclization process. The addition of iodide anions to the reaction mixture increased yields and selectivities especially when 2-bromobenzoates were employed. This phosphine-free one-pot synthesis features a high functional group tolerance and gives access to richly decorated isocoumarins. This general methodology was successful in the total synthesis of Xyridin A, an important natural product with antibacterial and antifungal activity.



Isocoumarins are one of the most important classes of organic compounds thanks to their widespread biological activities[1] and usefulness to build several pharmaceutical and natural products.[2] Traditional and, more recently, transition metal-catalyzed methods have been developed for the construction of isocoumarin scaffold.[3] The metal-catalyzed intramolecular annulation of benzoic acid derivatives bearing an alkyne in suitable position is probably the most popular approach.[3,4] The intermolecular version has been extensively investigated and several metals can be active in this transformation.[3,5] The atom economy is particularly high in the Rh or Ru/Cu-catalyzed oxidative annulation of alkynes by nonhalogenated carboxylic acids via a direct C−H bond activation.[6] However, this approach requires the use of expensive alkynes and manifests regioselectivity issues. Over the years, the use of diketones or vinyl acetates as coupling partners of benzoic acid has also received considerable attention.[7] Very recently, Zhang et al. have reported the synthesis of isocoumarins by Pd-catalyzed reaction of β-hydroxy carbonyl compounds with *ortho*-halobenzoates.[8] A palladium-catalyzed retro-aldol/α-arylation reaction provides the α-arylated carbonyl intermediates, which undergo intramolecular condensation with the ester moiety to obtain isocoumarin derivatives. Unfortunately this methodology suffers from some limitations, including low atom economy, the use of phosphine, high catalyst loading, and a limited substrate scope (Scheme 1, previous work). Taking advantage of our experience,[9] we now report a new and practical palladium-catalyzed synthesis of isocoumarins from 2-halobenzoates and ketones. This method features the α-arylation of the ketone and the intramolecular condensation with the ester group. We discuss for the first time the role of iodide anions in the synthesis of isocoumarins. The high accessibility of ketone derivatives together with other evident advantages (Scheme 1, this work) make this methodology a valuable alternative compared to existing ones. A direct and general route from ketones to isocoumarins is, up to now, unprecedented.[10]

Scheme 1. Pd-Catalyzed Syntheses of Isocoumarins from 2-Halobenzoates and Ketone Derivatives



At first, our investigations were focused in exploring the Pd-catalyzed annulation reaction of methyl 2-bromobenzoate **1a** with acetophenone **2a** (Table 1). In an initial experiment, **1a** (0.4 mmol) reacted with 5 equiv of acetophenone in dry DMF with 2.5 mol% of palladium acetate as catalyst and a mixture of K_2CO_3 and PhOK as bases (1.1 and 0.3 equiv. respectively). Mixtures were heated and samples periodically taken for analyses. The model reaction gave an encouraging 34% isolated yield of **3a** upon 24 h, mostly accompanied by unreacted starting material (Table 1, entry 1). Increasing the temperature proved beneficial for conversion and marginal for yield (entry 2,

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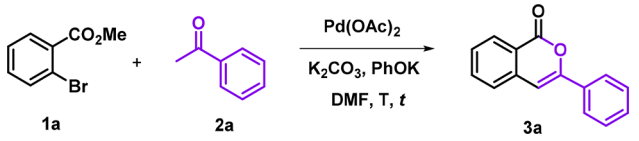
Table 1. Optimization of KI Amount and Reaction Conditions[a]



entry	KI (equiv)	T (°C)	t (h)	conv **1a** (%)[b]	yield **2a** (%)[b]
1		105	24	45	34
2		130	24	96	50
3	0.1	130	24	98	61
4	0.2	130	24	100	66
5	0.5	130	24	100	70
6	1.0	130	24	100	73
7	2.0	130	4	100	77
8	2.0	105	4	100	84[c]
9	2.0	80	24	37	31
10	4.0	105	4	62	39
11[d]	2.0	105	24		

[a]Reaction conditions: **1a** (0.4 mmol, 1 equiv), **2a** (5 equiv), $Pd(OAc)_2$ (2.5 mol%, 0.002 M), K_2CO_3 (1.1 equiv), PhOK (0.3 equiv) in DMF (4 mL) under N_2. [b]By GC. [c]Isolated yield. [d]No palladium source was used.

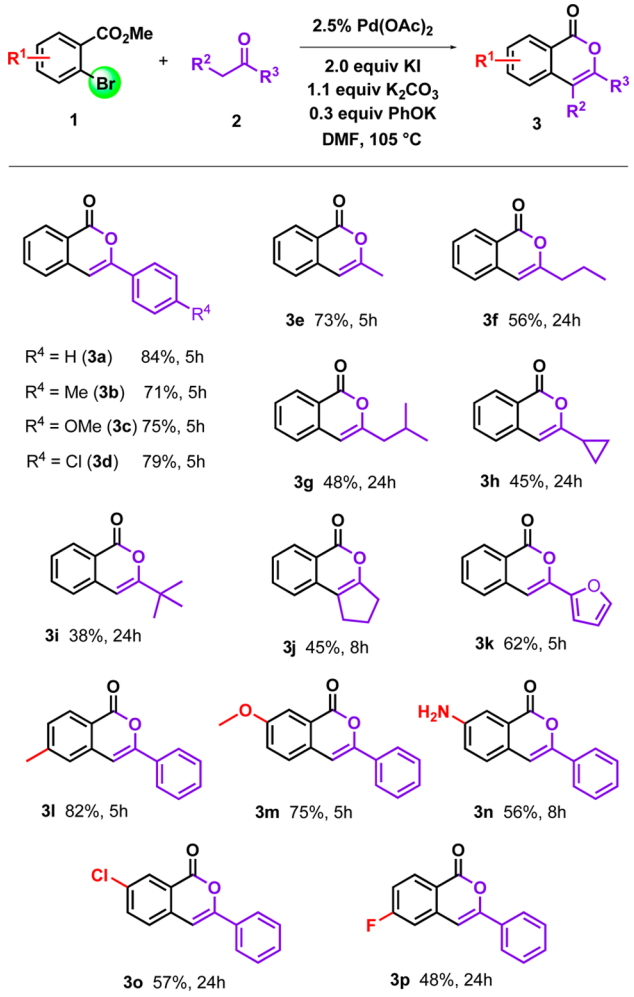
50%), reduction of **1a** to methyl benzoate and Ullmann-type coupling being undesired side reactions (25% and 20%, respectively).

An ample mix of tertiary phosphines proved ineffective to steer the outcome of this coupling. Similarly, various combinations of carbonates, phosphates, and alcoholates did not improve the yield of **3a**. We then resorted to test the effect of a source of iodide anions. The latter often serves indeed as reagent for metal-catalyzed halogen exchange reactions.[11] Iodide anions have been proposed as source of electrons,[12] which can serve to generate aryl radicals that add then on enolized ketones,[13] and might thus enable open-shell mechanisms.[14]

Addition of KI proved decisive in our case. Furthermore, our preliminary results strongly suggest that its actual role in these reactions differs from those named above. Substoichiometric amounts of KI showed an impact on the yield **3a** (entries 3−5, up to 70%). A further increase is observed increasing its concentration up to 2 equiv (entry 7, 77%). Reactions became significantly faster too, complete conversion requiring only 4 h. This enabled us to reduce back the temperature to 105 °C, delivering **3a** in 84% isolated yield (entry 8). Further modifications proved marginal (details in Table S1). No reaction took place without palladium (entry 11).

Once best conditions were secured, we studied scope and limitations of the reaction. Results are summarized in Scheme 2. Acetophenone could be decorated with various donating or withdrawing groups without hampering the outcome of the reactions (**3b−d**, 71−79%). Less acidic aliphatic ketones could be similarly employed, albeit at the expense of yield (**3e−j**, 38−73%). Noteworthy, ketones that have two different enolization sites provided a single regioisomer (**3f**, **3g**). The cyclopropyl ring remained untouched (**3h**). This result rules out mechanisms involving addition of aryl radicals on enolized ketones.[13] Methylene groups of cyclic ketones could be similarly arylated, enabling one to access fused tricycles (**3j**, 45%). Although the arylation of a furan could easily take place under similar conditions,[15] we managed to exclude this side-

Scheme 2. Catalytic Synthesis of Isocoumarins from 2-Bromobenzoates and Ketones[a,b]



[a]Reaction conditions: as Table 1, entry 8. [b]Isolated yield.

reaction to selectively obtain **3k** (62%). Switching to substituents on the bromide partner, electron-rich ones performed better (**3l−n**, 56−82%). Free amino groups are indeed tolerated, offering a valuable handle for further functionalization. Halo-coumarins could be prepared too (**3o−p**, 48−57%).

Wondering whether KI triggers a halogen-exchange reaction,[11] we tested methyl 2-iodobenzoates. They can be successfully employed as coupling partners in place of the corresponding bromides without KI (Scheme 3, values in parentheses show the relative difference with their bromide peers). In general, slightly lower yields were observed (by 5−9% for **3a-j**). This combines with shortened reaction times, usually within one to a few hours. Pinacolone and 2-acetylfurane provided **3i** and **3k** with +3% and +7%, respectively. Only traces of products were obtained with butyrophenone (**3q**, 10%).

The aryl iodide could be decorated with methyl groups (**3r−t**, 75−83%) and chloride ones (**3u**, 52%). A methoxy substituent *para* to iodide gave the worst outcome compared with its bromide peer (**3m**, Δ = −12%). Interestingly, heterocyclic iodides, such as thiophenes, also worked in this chemistry (**3v**, 64%).

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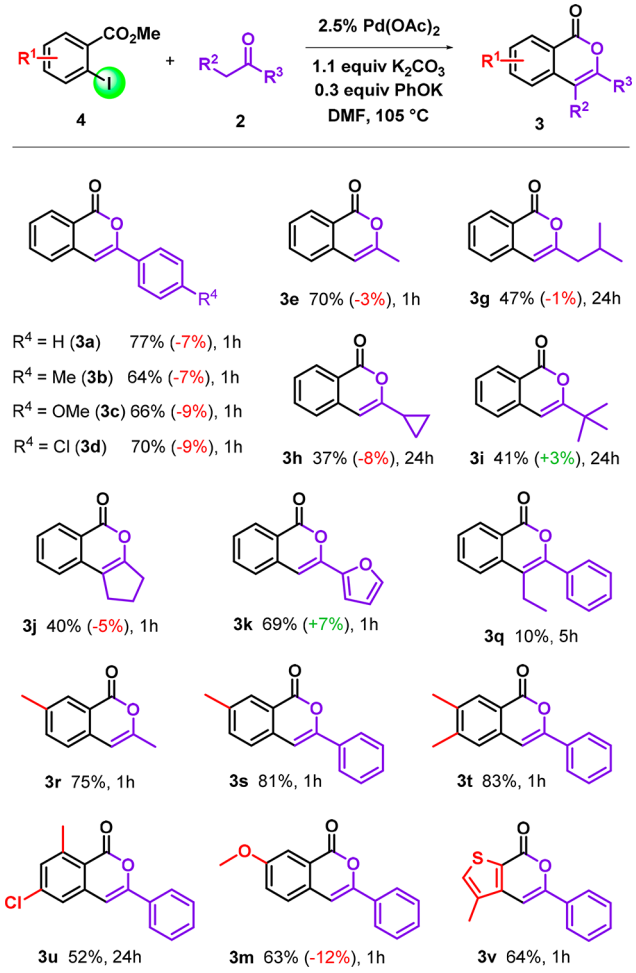
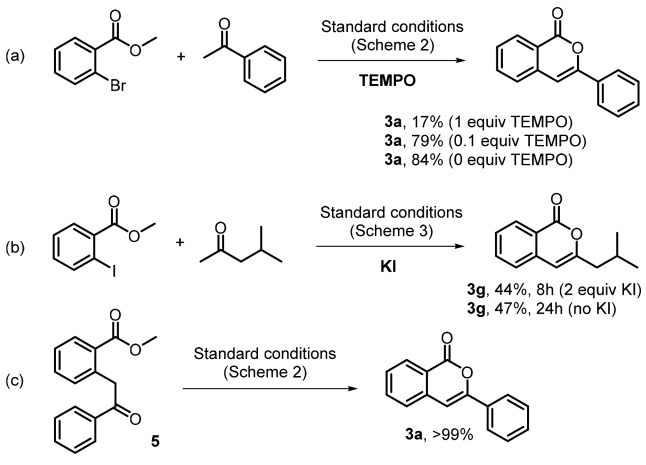
Scheme 3. Catalytic Synthesis of Isocoumarins from 2-Iodobenzoates and Ketones[a,b]



[a]Reaction conditions: as Table 1, entry 1. [b]Isolated yield.

Additional experiments were carried out in order to gain insights on the role of KI in this sequence and the reaction mechanism as well (Scheme 4). Reactivity is quenched by radical traps, as hindered phenols and TEMPO.[14] The yield of **3a** shrinks down to 17% performing the reaction with 1 equiv of TEMPO (Scheme 4a). This effect blurs at lower concentrations, as witnessed by retrieving 79% of **3a** with 0.1 equiv of TEMPO. We were however unable to identify any radical recombination product.[13,14] Moreover, the isolation of **3h** using both aryl-bromides and iodides together with the absence of products arising from cyclopropane ring-opening reduce the odds that phenoxide anions act as single electron donor[13] to trigger a radical ketone arylation mediated by DMF. More likely, TEMPO is able to oxidize the *in situ* formed Pd(0), decreasing the concentration of the active catalyst.

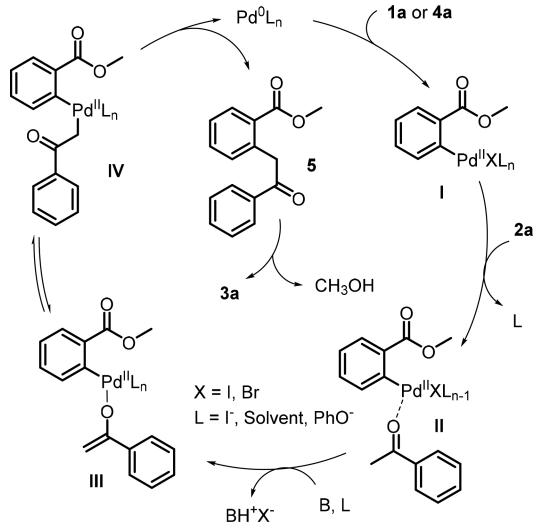
Scheme 4. Experimental Findings



Addition of KI to a reaction involving an aryl iodide (Scheme 4b) has a negligible impact on yield (44% against 47% without KI), in sharp contrast to observation with aryl bromides. On the contrary, the time required to consume the substrate did change significantly from 24 to 8 h. Since in this case no halogen exchange can be at work, the present result strongly supports that the role of iodide anions is crucial in the coordination of the metal providing anionic species able to increase the apparent reaction rate.[16] In addition when a further excess of KI was employed (Table 1, entry 10) the rate decreased drastically, suggesting that a too high concentration of iodides makes more difficult the coordination of the ketone, allowing side-reactions to take place.

Taken together all these results seem to exclude that KI serves as source of electrons.[12] Although the possibility that I^- anions operate as reagent for a halogen-exchange reaction[11] prior to ketone arylation cannot be ruled out, the observed acceleration in reactions involving aryl iodides suggests that iodide anions can act as ligands in this palladium-catalyzed phosphine-free synthesis of isocoumarins. According to these considerations we propose the pathway in Scheme 5.

Scheme 5. Proposed Pathway for the Pd-Catalyzed Synthesis of Isocoumarins from 2-Halobenzoates and Ketones



Oxidative addition of the Pd^0L_n with 2-halobenzoates **1a** or **4a** affords the Pd^{II} organometallic intermediate **I**. The ketone enters into the coordination sphere of palladium (**II**) and its subsequent deprotonation/enolization by the bases provides the Pd^{II} organometallic intermediate **III**, which is in equilibrium with **IV**.[17] Then, reductive elimination from intermediate **IV** gives the α-arylated ketone and regenerates the Pd^0L_n catalyst. As we have demonstrated (Scheme 4c) and in agreement with literature,[18] compound **5** yields isocoumarin **3a** and methanol as coproduct.

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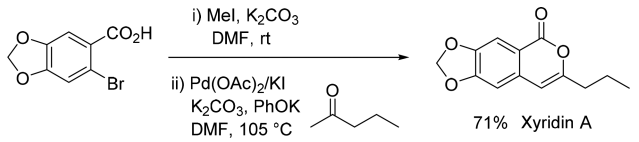
To further demonstrate the synthetic usefulness of our approach, Xyridin A[19] was synthesized in two steps from the corresponding commercial acid in 71% overall yield (Scheme 6). Quantitative esterification with iodomethane provided the

Scheme 6. Synthesis of Xyridin A



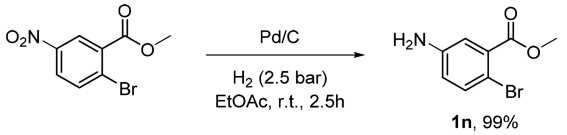
bromoester used for the coupling, which eventually delivered the desired natural product. This result shows that acetals are compatible with present methodology and further witness its generality.

In summary, we have described the first general methodology for the regioselective Pd-catalyzed synthesis of isocoumarins from 2-halobenzoates and ketones. The reaction makes direct use of simple and abundant ketones without the requirement of phosphine ligands or preformed diketones to generate richly decorated isocoumarins. The addition of iodide anions to the reaction mixture was crucial when 2-bromobenzoates were employed as starting materials. In view of the excellent regioselectivity, functional group tolerance, and simple protocol without expensive ligands, we expect widespread diffusion within the organic chemistry community.

EXPERIMENTAL SECTION

General Remarks. All chemicals were purchased from commercial sources and used as received, unless otherwise indicated. Acetone, DMF, and all other solvents were dried and stored over molecular sieves previously activated in oven at 300 °C overnight. Catalytic reactions were carried out under nitrogen using standard Schlenk technique. GC analyses were performed with an Agilent Tenchnologies 7820A equipped with a FID detector and a 30 m capillary column. GC-MS analyses (*m*/*z*, relative intensity %) were performed with an Agilent Technologies 6890N gas chromatograph coupled to an 5973N mass selective detector (Agilent Technologies) working at 70 eV ionizing voltage. Flash chromatography was carried out on an automated system (Combiflash Rf+ Lumen) using prepacked cartridges of silica (12 g Redi*Sep* Rf Columns). NMR spectra were recorded at 298 K, in $CDCl_3$ on a Bruker 400 MHz using the solvent as internal standard (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). The terms m, s, d, t, q, and quint represent multiplet, singlet, doublet, triplet, quadruplet, and quintuplet, respectively, and the term br means a broad signal. MS-ESI analyses were recorded on an Infusion Water Acquity Ultra Performance LC HO6UPS-823 M instrument (electrospray source, quadrupole analyzer). IR spectra were run on a Nicolet FT-IR 5700 spectrophotometer paired with a Diamond Smart Orbit accessory. Melting points were measured with an Electrothermal apparatus and are uncorrected. Elemental analyses were performed with a Carlo Erba EA 1108-Elemental Analyzer.

Preparation of Starting Materials. Methyl 2-bromobenzoate (**1a**),[20] methyl 2-bromo-4-methyl benzoate (**1l**),[21] methyl 2-bromo-5-methoxy benzoate (**1m**),[21] methyl 5-chloro-2-bromo benzoate (**1o**),[21] methyl 2-bromo-4-fluoro benzoate (**1p**),[21] methyl 2-iodo-5-methoxy benzoate (**4m**),[20] methyl 2-iodo-4,5-dimethyl benzoate (**4t**),[21] methyl 4-chloro-2-iodo-6-methyl benzoate (**4u**),[21] and 6-bromobenzo[d]-[1,3]dioxole-5-carboxylate[21] were prepared from the corresponding benzoic acids according to standard methods. Methyl 2-bromo-5-amino benzoate (**1n**) was obtained from methyl 2-bromo-5-nitro benzoate by hydrogenation as described below.



10% Pd/C (0.20 g) was added to a solution of methyl 2-bromo-5-nitro benzoate (1.5 g, 5.7 mmol) in EtOAc (40 mL) and the resulting mixture was stirred for 2.5 h at room temperature under 2.5 bar hydrogen pressure. After filtration through a Celite pad and removal of the solvent methyl 2-bromo-5-amino benzoate **1n** (1.3 g, 99%) was obtained as pale yellow oil. Spectroscopic data were consistent with those reported in the literature.[22]

General Procedure A. Catalyzed synthesis of isocoumarins **3** from methyl 2-bromo benzoates **1** (Scheme 2). A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with methyl 2-bromo benzoate (**1**, 0.4 mmol), ketone (**2**, 2 mmol), K_2CO_3 (0.45 mmol, 62 mg), PhOK (0.15 mmol, 20 mg), KI (0.8 mmol, 143 mg), $Pd(OAc)_2$ (2.5 mol%, 2.2 mg) in DMF (4 mL). The resulting mixture was stirred in an oil bath at 105 °C for 5−24 h. After cooling to room temperature, the reaction crude was filtered through a sand core funnel and washed with ethyl acetate (20 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.

General Procedure B. Catalyzed synthesis of isocoumarins **3** from methyl 2-iodo benzoates **4** (Scheme 3). A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with methyl 2-iodo benzoate (**4**, 0.4 mmol), ketone (**2**, 2 mmol), K_2CO_3 (0.45 mmol, 62 mg), PhOK (0.15 mmol, 20 mg), $Pd(OAc)_2$ (2.5 mol%, 2.2 mg) in DMF (4 mL). The resulting mixture was stirred in an oil bath at 105 °C for 1−24 h. After cooling to room temperature, the reaction crude was filtered through a sand core funnel and washed with ethyl acetate (20 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.

*3-Phenylisocoumarin (**3a**).* Following general procedure A, product **3a** was synthesized starting from methyl 2-bromo benzoate (**1a**, 86 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3a** (75 mg, 84% yield) as white solid. Spectroscopic data of **3a** were consistent with literature values.[7b] Compound **3a** was also obtained from methyl 2-iodo benzoate (106 mg) and acetophenone (240 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3a** (69 mg, 77% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.2 Hz, 1H), 7.88−7.83 (m, 2H), 7.71−7.66 (m, 1H), 7.49−7.39 (m, 5H), 6.89 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 153.5, 137.5, 134.9, 131.9, 129.9, 129.6, 128.8, 128.1, 126.0, 125.2, 120.5, 101.8; IR (neat) 1716 cm^{-1}; MS (ESI) calcd for $C_{15}H_{11}O_2$ $[M+H]^+$ *m*/*z* 223.08, found *m*/*z* 223.11.

*3-(4′-Methylphenyl)isocoumarin (**3b**).* Following general procedure A, product **3b** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 4-methyl acetophenone (268 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3b** (61 mg, 71% yield) as white solid. Spectroscopic data of **3b** were consistent with literature values.[23] Compound **3b** was also obtained from methyl 2-iodo benzoate (106 mg) and 4-methyl acetophenone (268 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3b** (61 mg, 64% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.2 Hz, 1H), 7.80−7.74 (m, 2H), 7.70 (td, J = 7.5, 1.3 Hz, 1H), 7.49−7.44 (m, 2H), 7.29−7.23 (m, 2H), 6.89 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 153.8, 140.3, 137.7, 134.8, 129.6, 129.5, 129.2, 127.9, 125.9, 125.2, 120.4, 101.1, 21.4; IR (neat) 1714 cm^{-1}; MS (ESI) calcd for $C_{16}H_{13}O_2$ $[M+H]^+$ *m*/*z* 237.09, found 237.12.

*3-(4′-Methoxyphenyl)isocoumarin (**3c**).* Following general procedure A, product **3c** was synthesized from methyl 2-bromo benzoate

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(**1a**, 86 mg) and 4-methoxy acetophenone (300 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3c** (76 mg, 75% yield) as white solid. Spectroscopic data of **3c** were consistent with literature values.[7b] Compound **3c** was also obtained from methyl 2-iodo benzoate (106 mg) and 4-methoxy acetophenone (300 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3c** (67 mg, 66% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.2 Hz, 1H), 7.79−7.73 (m, 2H), 7.65 (td, J = 7.5, 1.3 Hz, 1H), 7.45−7.38 (m, 2H), 6.96−6.89 (m, 2H), 6.77 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 161.0, 153.6, 137.9, 134.8, 129.5, 127.6, 126.7, 125.7, 124.4, 120.1, 114.2, 100.2, 55.4; IR (neat) 1736 cm^{-1}; MS (ESI) calcd for $C_{16}H_{13}O_3$ $[M+H]^+$ m/z 253.10, found m/z 253.15.

*3-(4′-Chlorophenyl)isocoumarin (**3d**).* Following general procedure A, product **3d** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 4-chloro acetophenone (308 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3d** (77 mg, 79% yield) as pale yellow solid. Spectroscopic data of **3d** were consistent with literature values.[24] Compound **3d** was also obtained from methyl 2-iodo benzoate (106 mg) and 4-chloro acetophenone (308 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3d** (72 mg, 70% yield) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 8.3 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 6.87 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 152.4 137.2, 135.9, 134.9, 130.4, 129.6, 129.1, 128.4, 126.4, 126.0, 120.5, 102.0; IR (neat) 1722 cm^{-1}; MS (ESI) calcd for $C_{15}H_{10}O_2Cl$ $[M+H]^+$ m/z 257.04, found m/z 257.12.

*3-Methylisocoumarin (**3e**).* Following general procedure A, product **3e** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and acetone (116 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3e** (47 mg, 73% yield) as white solid. Spectroscopic data of **3e** were consistent with literature values.[7b] Compound **3e** was also obtained from methyl 2-iodo benzoate (106 mg) and acetone (116 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3e** (45 mg, 70% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 6.25 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 154.5, 137.6, 134.7, 129.7, 127.5, 124.9, 119.9, 103.5, 19.6; IR (neat) 1714 cm^{-1}; MS (ESI) calcd for $C_{10}H_9O_2$ $[M+H]^+$ m/z 161.06, found m/z 161.12.

*3-Propylisocoumarin (**3f**).* Following general procedure A, product **3f** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and pentan-2-one (170 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3f** (42 mg, 56% yield) as pale colorless oil. Spectroscopic data of **3f** were consistent with literature values.[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 8.0, 0.6 Hz, 1H), 7.67 (td, J = 7.8, 1.3 Hz, 1H), 7.45 (td, J = 7.9, 1.3 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 6.26 (s, 1H), 2.51 (t, J = 7.5 Hz, 2H), 1.80−1.71 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 158.1, 137.6, 134.7, 129.5, 127.5, 125.0, 120.2, 103.0, 35.4, 20.2, 13.5; IR (neat) 1721 cm^{-1}; MS (ESI) calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ 189.09, found m/z 189.20.

*3-(2-Methylpropyl)isocoumarin (**3g**).* Following general procedure A, product **3g** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 4-methylpentan-2-one (200 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3g** (39 mg, 48% yield) as pale yellow oil. Compound **3g** was also obtained from methyl 2-iodo benzoate (106 mg) and 4-methylpentan-2-one (200 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3g** (39 mg, 47% yield) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.1 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 6.25 (s, 1H), 2.38 (d, J = 7.2 Hz, 2H), 2.20−2.10 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 157.4, 137.6, 134.7, 129.5, 127.6, 125.0, 120.1, 104.0, 42.8, 26.6, 22.2; IR (neat) 1718 cm^{-1}; MS (ESI) calcd for $C_{13}H_{15}O_2$ $[M+H]^+$ m/z 203.11, found m/z 203.17; Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98; O, 15.82. Found: C, 77.06; H, 7.03.

*3-Cyclopropylisocoumarin (**3h**).* Following general procedure A, product **3h** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and methyl cyclopropyl ketone (170 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3h** (34 mg, 45% yield) as pale yellow oil. The spectroscopic data of **3h** were consistent with literature values.[26] Compound **3h** was also obtained from methyl 2-iodo benzoate (106 mg) and methyl cyclopropyl ketone (170 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3h** (28 mg, 37% yield) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 1H), 7.67−7.61 (m, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 6.29 (s, 1H), 1.84−1.76 (m, 1H), 1.09−1.03 (m, 2H), 0.95−0.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 158.4, 137.9, 134.8, 129.5, 127.1, 124.6, 119.9, 101.4, 13.8, 7.0; IR (neat) 1715 cm^{-1}; MS (ESI) calcd for $C_{12}H_{11}O_2$ $[M+H]^+$ m/z 187.08, found m/z 187.17.

*3-tert-Butylisocoumarin (**3i**).* Following general procedure A, product **3i** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and pinacolone (200 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3i** (31 mg, 38% yield) as pale yellow oil. Spectroscopic data of **3i** were consistent with literature values.[27] Compound **3i** was also obtained from methyl 2-iodo benzoate (106 mg) and pinacolone (200 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3i** (34 mg, 41% yield) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 6.32 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 163.0, 137.7, 134.6, 129.4, 127.6, 125.5, 120.1, 99.7, 35.6, 28.0; IR (neat) 1718 cm^{-1}; MS (ESI) calcd for $C_{13}H_{15}O_2$ $[M+H]^+$ m/z 203.11, found m/z 203.18.

*2,3-Dihydro-1H-cyclopenta[c]isochromen-5-one (**3j**).* Following general procedure A, product **3j** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and cyclopentanone (168 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3j** (34 mg, 45% yield) as white solid. Spectroscopic data of **3j** were consistent with literature values.[28] Compound **3j** was also obtained from methyl 2-iodo benzoate (106 mg) and cyclopentanone (168 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3j** (30 mg, 40% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (further split d, J = 8.0 Hz, 1H), 7.69 (td, J = 7.9, 1.1 Hz, 1H), 7.42 (td, J = 8.1, 1.1 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 2.87−2.78 (m, 4H), 2.22−2.12 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 156.0, 136.4, 134.8, 130.4, 127.0, 122.5, 119.6, 113.3, 31.0, 26.5, 19.8; IR (neat) 1716 cm^{-1}; MS (ESI) calcd for $C_{12}H_{11}O_2$ $[M+H]^+$ 187.08, found m/z 187.15.

*3-(2-Furanyl)isocoumarin (**3k**).* Following general procedure A, product **3k** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 2-acetylfuran (220 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3k** (52 mg, 62% yield) as orange solid. Spectroscopic data of **3k** were consistent with literature values.[27] Compound **3k** was also synthesized from methyl 2-iodo benzoate (106 mg) and 2-acetylfuran (220 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3k** (59 mg, 69% yield) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.2 Hz, 1H), 7.68 (td, J = 7.8, 1.3 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H),

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7.47−7.42 (m, 2H), 6.93 (d, J = 3.4 Hz, 1H), 6.83 (s, 1H), 6.52 (dd, J = 3.4, 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 146.9, 146.1, 144.0, 137.3, 135.0, 129.8, 128.0, 126.0, 120.4, 112.1, 110.1, 100.0; IR (neat) 1731 cm^{-1}; MS (ESI) calcd for $C_{13}H_9O_3$ $[M+H]^+$ m/z 213.06, found m/z 213.14.

*6-Methyl-3-phenylisocoumarin (**3l**).* Following general procedure A, product **3l** was synthesized from methyl 2-bromo-4-methyl benzoate (**1l**, 92 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3l** (78 mg, 82% yield) as white solid. Spectroscopic data of **3l** were consistent with literature values.[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.1 Hz, 1H), 7.83 (dd, J = 8.0, 1.6 Hz, 2H), 7.47−7.36 (m, 3H), 7.27−7.20 (m, 2H), 6.82 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 153.5, 145.9, 137.6, 132.0, 129.8, 129.51, 129.49, 128.8, 126.0, 125.2, 118.1, 101.5, 21.9; IR (neat) 1712 cm^{-1}; MS (ESI) calcd for $C_{16}H_{13}O_2$ $[M+H]^+$ m/z 237.09, found m/z 237.17.

*7-Methoxy-3-phenylisocoumarin (**3m**).* Following general procedure A, product **3m** was synthesized from methyl 2-bromo-5-methoxy benzoate (**1m**, 98 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3m** (76 mg, 75% yield) as pale yellow solid. Spectroscopic data of **3m** were consistent with literature values.[27] Compound **3m** was also synthesized from methyl 2-iodo-5-methoxy benzoate (**4m**, 117 mg) and acetophenone (240 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3m** (64 mg, 63% yield) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.83 (m, 2H), 7.72 (d, J = 2.7 Hz, 1H), 7.48−7.37 (m, 4H), 7.31 (dd, J = 8.6, 2.7 Hz, 1H), 6.92 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 159.6, 151.7, 132.1, 131.2, 129.6, 128.8, 127.6, 124.9, 124.7, 121.7, 110.0, 101.6, 55.8; IR (neat) 1733 cm^{-1}; MS (ESI) calcd for $C_{16}H_{13}O_3$ $[M+H]^+$ m/z 253.09, found m/z 253.17.

*7-Amino-3-phenylisocoumarin (**3n**).* Following general procedure A, product **3n** was synthesized from methyl 2-bromo-5-amino benzoate (**1n**, 92 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3n** (53 mg, 56% yield) as pale yellow solid. Mp 171−173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.82 (m, 2H), 7.56 (d, J = 2.4 Hz, 1H), 7.47−7.42 (m, 2H), 7.42−7.36 (m, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.08 (dd, J = 8.3, 2.5 Hz, 1H), 6.89 (s, 1H), 4.05 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 150.4, 146.9, 132.4, 129.2, 128.8, 127.4, 124.7, 122.9, 121.9, 112.7, 102.0; IR (neat) 1728 cm^{-1}; MS (ESI) calcd for $C_{15}H_{11}NO_2$ $[M]^+$ m/z 237.08, found m/z 237.14; Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90; O, 13.49. Found: C, 76.11; H, 4.61; N, 5.84.

*7-Chloro-3-phenylisocoumarin (**3o**).* Following general procedure A, product **3o** was synthesized from methyl 5-chloro-2-bromo benzoate (**1o**, 100 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3o** (59 mg, 57% yield) as pale yellow solid. Spectroscopic data of **3o** were consistent with literature values.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 1.8 Hz, 1H), 7.93−7.86 (m, 2H), 7.69 (dd, J = 8.3, 2.0 Hz, 1H), 7.53−7.44 (m, 4H), 6.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.2, 154.0, 135.9, 135.3, 133.9, 131.6, 130.3, 129.2, 128.9, 127.5, 125.3, 121.7, 101.0; IR (neat) 1722 cm^{-1}; MS (ESI) calcd for $C_{15}H_{10}ClO_2$ $[M+H]^+$ m/z 257.04, found m/z 257.15.

*6-Fluoro-3-phenylisocoumarin (**3p**).* Following general procedure A, product **3p** was synthesized from methyl 2-bromo-4-fluoro benzoate (**1p**, 94 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3p** (46 mg, 48% yield) as white solid. Spectroscopic data of **3p** were consistent with literature values.[7b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 8.7, 5.6 Hz, 1H), 7.93−7.86 (m, 2H), 7.52−7.45 (m, 3H), 7.24−7.13 (m, 2H), 6.93 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (d, $J_{C,F}$ = 256.5 Hz), 161.4, 154.9, 140.24 (d, $J_{C,F}$ = 10.8 Hz), 133.03 (d, $J_{C,F}$ = 10.4 Hz), 131.6, 130.4, 128.9, 125.4, 117.0, 116.46 (d, $J_{C,F}$ = 23.4 Hz), 111.52 (d, $J_{C,F}$ = 22.6 Hz), 101.22 (d, $J_{C,F}$ = 2.9 Hz); IR (neat) 1723 cm^{-1}; MS (ESI) calcd for $C_{15}H_{10}FO_2$ $[M+H]^+$ m/z 241.07, found m/z 241.15.

*3-Phenyl-4-ethylisocoumarin (**3q**).* Following general procedure B, product **3q** was synthesized from methyl 2-iodo benzoate (106 mg) and 1-phenylbutanone (296 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3q** (10 mg, 10% yield) as pale yellow solid. Mp 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, J = 7.9, 0.9 Hz, 1H), 7.83 (td, J = 8.6, 1.4 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.62−7.45 (m, 6H), 2.75 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 151.3, 137.7, 134.7, 133.5, 130.1, 129.4, 129.0, 128.4, 127.8, 123.4, 121.4, 115.2, 20.1, 14.7; IR (neat) 1721 cm^{-1}; MS (ESI) calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ m/z 251.11, found m/z 251.21; Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; O, 12.78. Found: C, 81.43; H, 5.70.

*7-Methyl-3-methylisocoumarin (**3r**).* Following general procedure B, product **3r** was synthesized from methyl 2-iodo-5-methyl benzoate (110 mg) and acetone (116 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3r** (52 mg, 75% yield) as white solid. Spectroscopic data of **3r** were consistent with literature values.[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (further split s, 1H), 7.48 (dd, J = 8.0, 1.5 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.22 (s, 1H), 2.44 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 153.6, 137.7, 136.0, 135.2, 129.1, 124.8, 119.8, 103.4, 21.3, 19.5; IR (neat) 1712 cm^{-1}; MS (ESI) calcd for $C_{11}H_{11}O_2$ $[M+H]^+$ 175.08, found m/z 175.18.

*7-Methyl-3-phenylisocoumarin (**3s**).* Following general procedure B, product **3s** was synthesized from methyl 2-iodo-5-methyl benzoate (110 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3s** (76 mg, 81% yield) as white solid. Spectroscopic data of **3s** were consistent with literature values.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.83 (d, J = 7.6 Hz, 2H), 7.51−7.33 (m, 5H), 6.88 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 152.7, 138.5, 136.1, 135.0, 132.0, 129.7, 129.3, 128.8, 125.9, 125.1, 120.4, 101.7, 21.4; IR (neat) 1712 cm^{-1}; MS (ESI) calcd for $C_{16}H_{13}O_2$ $[M+H]^+$ 237.09, found m/z 237.18.

*6,7-Dimethyl-3-phenylisocoumarin (**3t**).* Following general procedure B, product **3t** was synthesized from methyl 2-iodo-4,5-dimethyl benzoate (**4t**, 116 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3t** (87 mg, 83% yield) as white solid. Spectroscopic data of **3t** were consistent with literature values.[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.87 (d, J = 7.7 Hz, 2H), 7.48−7.40 (m, 3H), 7.25 (s, 1H), 6.87 (s, 1H), 2.38 (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 152.9, 145.2, 137.8, 135.6, 132.2, 129.7, 129.6, 128.8, 126.6, 125.1, 118.4, 101.6, 20.4, 19.8; IR (neat) 1712 cm^{-1}; MS (ESI) calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ 251.11, found m/z 251.20.

*6-Chloro-8-methyl-3-phenylisocoumarin (**3u**).* Following general procedure B, product **3u** was synthesized from methyl 4-chloro-2-iodo-6-methyl benzoate (**4u**, 124 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3u** (57 mg, 52% yield) as white solid. Mp 158−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.86 (m, 2H), 7.52−7.44 (m, 3H), 7.32 (d, J = 1.9 Hz, 1H), 7.26 (further split s, 1H), 6.82 (s, 1H), 2.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 154.4, 145.7, 140.5, 140.2, 131.6, 130.9, 130.2, 128.9, 125.3, 123.5, 117.3, 101.3, 23.0; IR (neat) 1716 cm^{-1}; MS (ESI) calcd for $C_{16}H_{12}ClO_2$ $[M+H]^+$ 271.05, found m/z 271.15; Anal. Calcd for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.10; Cl, 13.10; O, 11.82. Found: C, 71.13; H, 4.15.

*3-Methyl-5-phenyl-7H-thieno[2,3-c]pyran-7-one (**3v**).* Following general procedure B, product **3v** was synthesized from methyl 3-iodo-4-methylthiophene-2-carboxylate (113 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3v** (72

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mg, 64% yield) as pale orange solid. Mp 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.2, 1.2 Hz, 2H), 7.49−7.41 (m, 4H), 7.00 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 156.3, 147.2, 134.0, 132.4, 132.0, 130.1, 128.9, 125.4, 122.9, 97.6, 13.7; IR (neat) 1704 cm^{-1}; MS (ESI) calcd for $C_{14}H_{11}O_2S$ $[M+H]^+$ 243.05, found m/z 243.15; Anal. Calcd for $C_{14}H_{10}O_2S$: C, 69.40; H, 4.16; O, 13.21; S, 13.23. Found: C, 69.28; H, 4.09.

Synthesis of Xyridine A (Scheme 6). (i) 6-Bromobenzo[d][1,3]-dioxole-5-carboxylate was synthesized from the corresponding benzoic acids according to literature.[21] (ii) A Schlenk-type flask, equipped with a magnetic stirring bar was charged, under nitrogen, with methyl 6-bromobenzo[d][1,3]dioxole-5-carboxylate (122 mg, 0.4 mmol), pentan-2-one (170 mg, 2 mmol), K_2CO_3 (0.45 mmol, 62 mg), PhOK (0.15 mmol, 20 mg), KI (0.8 mmol, 142.8 mg), $Pd(OAc)_2$ (2.5 mol%, 2.2 mg) in DMF (4 mL). The resulting mixture was stirred in an oil bath at 105 °C for 5 h. After cooling to room temperature, the reaction crude was filtered through a sand core funnel and washed with ethyl acetate (20 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using hexane-EtOAc as eluent to afford Xyridine A as white solid (66 mg, 71%). Spectroscopic data were consistent with reported values.[19b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.72 (s, 1H), 6.15 (s, 1H), 6.08 (s, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.79−1.66 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 157.1, 153.6, 147.8, 135.3, 114.6, 107.3, 103.6, 103.0, 102.1, 35.3, 20.3, 13.5; IR (neat) 1739 cm^{-1}; MS (ESI) calcd for $C_{13}H_{13}O_4$ $[M+H]^+$ 233.08, found m/z 233.18.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01355.

Optimization study and copy of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nicola.dellaca@unipr.it

*E-mail: elena.motti@unipr.it

ORCID

Giovanni Maestri: 0000-0002-0244-8605

Nicola Della Ca': 0000-0002-7853-7954

Notes

The authors declare no competing financial interest.

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