Ipso Substitution as a Route to Benzo[*c*]quinolizines and 4-Hydroxycoumarins

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A convenient ipso substitution method for the preparation of benzo[*c*]quinolizine (**2**) and 4-hydroxy-3-(2′-pyridyl)coumarin (**3**) has been developed. The intramolecular nucleophilic substitution reaction of 3-oxo-2-(2′-pyridyl)-(2-halophenyl)propanoate (**1**) in refluxing xylenes gives initially benzo[*c*]-quinolizine, while further heating results in the formation of 4-hydroxycoumarin. A mechanism has been proposed to rationalize the two competitive reaction pathways, and the role of HCl is discussed. Under optimized conditions, seven benzo[*c*]quinolizines and five coumarins were prepared in moderate to good yields.

Introduction

Cystic fibrosis (CF) is caused by mutations in the CF transmembrane conductance regulator (CFTR) protein, a cAMP-regulated epithelial cell membrane selective chloride ion channel.[1] An important goal in CF research is the identification of small organic molecule activators of CFTR, several classes of which have been discovered including benzo[*c*]quinolizinium[2] and flavones.[3] Figure 1 shows the structure of the most potent compound from each class, **MPB-07** and **UC$_{CF}$-029**, respectively. Given the significance of the CF problem, one objective of our research has been to prepare combinatorial libraries based on these lead compounds and subsequently apply high-throughput screening technology with the goal of discovering novel CFTR activators.[4]

In a recent communication,[5] we reported that *β*-ketoester **1** undergoes a novel intramolecular nucleophilic aromatic substitution reaction in refluxing xylenes (Figure 2) to deliver the unexpected[2] coumarin product **3**, the first reported coumarin[6] with a 3-(pyridin-2-yl) substituent. Indeed, we had expected **1** to cyclize via the pyridine-*N* to 6*H*-benzo[*c*]quinolizin-6-one (**2**).[7] Coumarins[8]

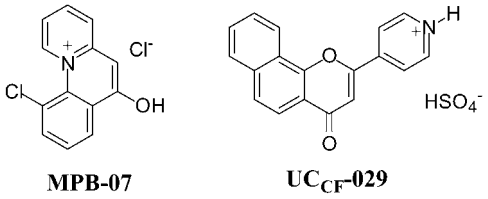

Figure 1. Small molecule CFTR activators.

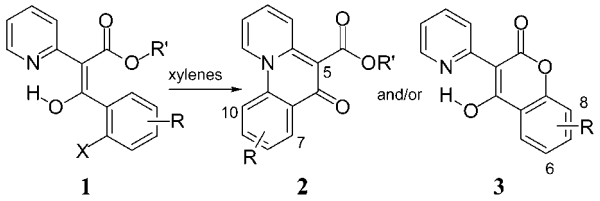

Figure 2. Ipso substitution products from **1**.

are found in nature, often as a structural subunit in more complex natural products. They are reported to evoke a broad range of biological activities and are also widely used as food constituents (antioxidants and stabilizers), as immunomodulatory substances, and as fluorescent markers with applications in analyses, lasers, and clinical studies. The simplest method for making 3-aryl-4-hydroxycoumarins is by direct C-3 arylation[9] of a performed coumarin ring, but this direct arylation normally requires organometallic compounds that limit the aryl groups. This interesting and, to our knowledge, unprecedented intramolecular ipso substitution by a carboxy group (**1**→**3**) prompted us to further investigate the scope of this reaction with the aim of defining conditions wherein *β*-ketoester **1** can be manipulated to reliably deliver either the benzo[*c*]quinolizine (**2**) or the coumarin (**3**) product.

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(7) Indeed, in one case reported in ref 5, ipso substitution did lead to the anticipated benzo[*c*]quinolizine product (**2a**−**3a**).

(8) *Coumarins, Biology, Applications and Mode of Action*; O′Kennedy, R., Thornes, R. D., Eds.; John Wiley and Sons: New York, 1997.

(9) (a) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *Tetrahedron Lett*. **1989**, *30*, 1539−1542. (b) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1365−1375.

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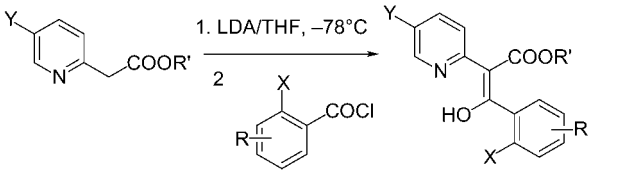
Table 1. Preparation of 3-Oxo-2-(2′-pyridyl)-3-(2′-halophenyl)propanoates



compd	R′	X	R	Y	yield	compd	R′	X	R	Y	yield
1a	Bn	Cl	H	H	69%	**1g**	Bn	Br	3-NO_2	H	68%
1b	Bn	Br	H	H	65%	**1h**	Bn	Br	5-NO_2	H	60%
1c	Bn	Cl	3-Cl	H	56%	**1i**	Me	Cl	4-Cl	H	71%
1d	Bn	Cl	4-Cl	H	75%	**1j**	Me	Cl	6-Cl	H	51%
1e	Bn	Cl	6-Cl	H	53%	**1k**	Bn	Cl	4-Cl	Br	85%
1f	Bn	Cl	5-CF_3	H	70%						

Results and Discussion

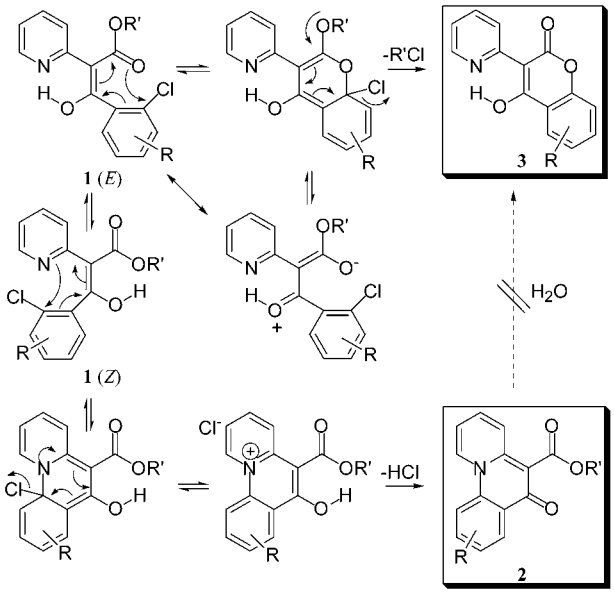
3-Oxo-2-(2′-pyridyl)-3-(2′-halophenyl)propanoates (**1**), the precursor to both classes of compounds (**2** and **3**), were easily prepared by C-acylation of 2-pyridyl acetates as shown in Table 1. The isolated yields are generally moderate (50−85%) as most substituted benzoyl chlorides were prepared from the corresponding benzoic acids by refluxing in $SOCl_2$ and used without further purification. Higher yields were achieved when commercial 2-halobenzoyl chlorides were available, i.e., compounds **1d** and **1i**. Several dichlorobenzoyl chlorides were chosen because the benzo[*c*]quinoliziniums with the highest CFTR activity are those with chloro-substituents at C-7 and/or C-10.[3]

The starting material, benzyl 2-pyridyl acetate, was previously synthesized[10] by the transesterification of methyl 2-pyridyl acetate with lithium benzoxide. Direct benzyl esterification of commercially available 2-pyridylacetic acid hydrochloride under either acid conditions or basic DCC coupling conditions generally gave low yields, presumably due to the low solubility of the pyridinium salts in organic solvents. In our hands, the most practical method for preparing substituted benzyl-2-pyridyl acetate is by nucleophilic substitution of benzyl chloride with 2-pyridylacetic acid hydrochloride in the presence of 2 equiv of cesium carbonate and a catalytic amount of KI in warm DMF. The isolated yield is generally >80%.

We next turned our attention to the key intramolecular ipso substitution step (Figure 2). Various 3-oxo-2-(2′-pyridyl)-3-(2′-halophenyl)propanoates **1** were heated in xylenes at reflux for 2−24 h. After removal of the solvent in a vacuum, the crude product was purified by recrystallization or by silica gel chromatograghy. Both products (**2** and **3**) were obtained as high melting point crystalline solids. It is also interesting to note that all of the benzo[*c*]quinolizines and 4-hydroxycoumarins reported here are fluorescent and range from pale yellow to orange in color.

On closer inspection of the product ratios and yields for these competing ipso substitution reactions, we observed that substituents on the benzene ring play an important role in determining the course of the reaction. When the ortho-halo substituent is a bromine and when a strong electron-withdrawing nitro group is incorporated at the ortho- or para-positions relative to the bromine, the reaction proceeds rapidly to the 4-hydroxycoumarin product. However, the cyclization reaction is slower when the phenyl ring bears two chloro substituents and, as

Scheme 1. Proposed Mechanism for the Reaction of 1 in Refluxing Xylenes



indicated by TLC in ethyl acetate, the benzo[*c*]quinolizine product (**2**) is formed initially. This kinetic product then slowly converts to the thermodynamic 4-hydroxycoumarin product (**3**), which precipitates from xylenes.

The following mechanism (Scheme 1) is proposed to rationalize these observations. Starting β-ketoester **1** exists in a highly enolized, hydrogen bonded form [**1**(*Z*) and **1**(*E*)]. The enol proton generally appears at 18 ppm in the ^{1}H NMR spectrum. At elevated temperatures, the *E*- and *Z*-enol forms of **1** are in rapid equilibrium. Intramolecular nucleophilic attack by either the pyridine-*N* or the ester-*O* (the depicted resonance contributor serves to both activate the aromatic ring and increase *O*-nucleophilicity) occurs as a concerted process to form a six-membered ring intermediate that allows maximum π-electron delocalization. This type of concerted process was previously proposed by Viefond[11] to account for the quaternization reaction of pyridine. This relatively slow cyclization step is followed by the loss of HX (X = Cl or Br) gas in the benzo[*c*]quinolizine pathway or by the loss of R′X in the coumarin pathway. One could also imagine that coumarin **3** is formed directly from benzo[*c*]quinolizine **2** by a process consisting of addition of water to the aryl ring of **2** followed by opening of the central pyridine ring to give a phenol that could undergo a subsequent intramolecular transesterification. However, **2c** is unchanged upon being heated in *o*-xylene-d_{10} (140 °C, 12 h; sealed NMR tube).

Our proposed mechanism indicates that HX plays an important role in mediating the competition between these two pathways. On one hand, the HX accelerates the coumarin pathway by catalyzing hydrolysis of the ester with concomitant release of R′X. On the other hand, HX is released in the benzo[*c*]quinolizine pathway as a side product and its accumulation would slow formation of **2** (i.e., by reversion of intermediates back to **1**). The various roles of HX in a "closed vessel" reaction provide a good explanation for the initial formation of benzo[*c*]-quinolizine **2** followed by its slow conversion into hydroxycoumarin **3**.

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(11) Vierfond, J.-M.; Mettey, Y.; Joubin, R.; Miocque, M. *J. Heterocycl. Chem.* **1979**, *16*, 753−755.

Table 2. Intramolecular Ipso Substitution in 3-Oxo-2-(2′-pyridyl)-3-(2′-halophenyl)propanoates

entry	starting material	X	R′	R[a]	Y	condition[b]	reaction time (h)	major product (isolated yield)
1	**1a**	Cl	Bn	H	H	A	20	**2a** (45%)[c]
2	**1b**	Br	Bn	H	H	B	3	**3b** (72%)
3	**1c**	Cl	Bn	3-Cl	H	A	9	**2c** (50%)[d]
4	**1d**	Cl	Bn	4-Cl	H	A	2	**2d** (82%)
5	**1d**	Cl	Bn	4-Cl	H	B	24	**3d** (65%)[d]
6	**1e**	Cl	Bn	6-Cl	H	A	21	**2e** (40%)[d]
7	**1f**	Cl	Bn	5-CF_3	H	A	4	**2f** (69%)
8	**1f**	Cl	Bn	5-CF_3	H	B	6	**3f** (88%)
9	**1g**	Br	Bn	3-NO_2	H	B	2	**3g** (84%)
10	**1h**	Br	Bn	5-NO_2	H	B	2	**3h** (96%)
11	**1i**	Cl	Me	4-Cl	H	A	2.5	**2i** (89%)
12	**1j**	Cl	Me	6-Cl	H	A	4	**2j** (55%)[d]
13	**1k**	Cl	Bn	4-Cl	Br	A	2	**2k** (54%)[d]

[a] Substituents are numbered as in the starting materials. [b] Condition A: open reaction tube. Condition B: sealed tube. Refer to the Experimental Section for details. [c] There was 15% of **3b** as a minor product. [d] There was unreacted starting material plus a small amount of product **3**.

If these assumptions are operative, we surmised that experimental control of the HX concentration would facilitate product selection. To test this idea, two thick glass test tubes containing equal amounts of **1i** in xylenes were heated (oil bath temperature = 150 °C). One tube (Rxn A) was open to the atmosphere and bubbled with a low flow of nitrogen gas. The other tube (Rxn B) was sealed with a Teflon screw cap. After 2.5 h, the reaction mixtures in both tubes were cooled to room temperature and worked up following our standard procedures. As anticipated, Rxn A gave benzo[*c*]quinolizine **2i** as the sole product (89% isolated yield), while Rxn B gave **2i** and hydroxycoumarin **3d** in 43 and 15% isolated yields, respectively.

With this information in hand, we next applied our HX hypothesis to studies aimed at controlling the product distribution of benzo[*c*]quinolizine versus hydroxycoumarin. Optimized reaction conditions and product yields are shown in Table 2. In addition to HX concentration, substituent R on the benzene ring plays a predominant role in determining the reaction course. The nature of X (Cl versus Br) and the ester alkyl group (R′) also figure into the reaction time and product yields. In general, coumarin formation is favored by strong electron-withdrawing groups for R and by employing Br over Cl as the ipso leaving group. Benzo[*c*]quinolizines, kinetic products in these competitive ipso substitution reactions, are isolated as the major product with less reactive propanoate substrates. These kinetic benzo[*c*]quinolizines are converted into the thermodynamic hydroxycoumarin products if the reaction mixture is heated for a prolonged time. Unfortunately, prolonged heating also results in a greater extent of decomposition, making this an impractical method for preparing coumarins from less reactive propanoate substrates.

We were also interested in learning how substitution on the pyridine ring in **1** would affect its cyclization; in particular, we wanted to know whether an electron-withdrawing substituent would reduce the nucleophilicity of the pyridine-*N* to the point that only coumarin product would be obtained. However, since the requisite substituted pyridine acetic acids are not readily available, we limited ourselves to the investigation of **1k** (Y = Br), which was prepared from 5-bromopyridine acetic acid.[12] Heating this substrate in refluxing xylenes for 2 h gave benzo[*c*]quinolizine **2k** in 54% yield, indeed a reduced yield of benzo[*c*]quinolizine product when compared to that of **1d** (Y = H; →**2d** in 82% yield in 2 h), while prolonged (24 h) heating in a sealed tube led primarily to decomposition (no benzo[*c*]quinolizine product and <10% of what appears to be the coumarin product).

Conclusion

We have established a convenient method for the production of benzo[*c*]quinolizine and 4-hydroxy-3-(2′-pyridyl)coumarin derivatives from the same 3-oxo-2-(2′-pyridyl)-3-(2′-halophenyl)propanoate precursors by controlling the course of two competing intramolecular nucleophilic aromatic substitution reactions. Strong electron-withdrawing groups on the electrophilic aromatic moiety favor the formation of the 4-hydroxy-3-(2′-pyridyl)-coumarins. The yield of benzo[*c*]quinolizine derivatives can be increased significantly by removing the HX gas formed during the ipso substitution reaction. Both classes of compounds have been submitted for CFTR screening, and their biological activities will be reported in due course. The solid-phase synthesis of a larger library of these compounds is currently underway.

Experimental Section

General Experimental Procedures. Unless otherwise noted, starting materials were obtained from commercial suppliers and used as received. THF was freshly distilled from sodium/benzophenone. Melting points were determined using an electrothermal 9100 apparatus and are uncorrected. Infrared spectra were taken neat (solids) on a refractive spectrophotometer. ^{1}H NMR was measured at 400 or 300 MHz, and ^{13}C NMR was taken at 100 or 75 MHz in the solvent indicated. Elemental analyses were performed by Midwest Microlabs.

C-Acylation of 2-Pyridyl Acetate (1): General Procedure. A solution of lithium diisopropylamide (2.4 mmol) in dry THF (6 mL) was cooled to −78 °C under nitrogen. A solution of 2-(2′-pyridyl)acetate (2.0 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min at which time a solution of the appropriate benzoyl chloride (2.0 mmol) in dry THF (2 mL) was added slowly. Stirring was continued at 0 °C for an additional 30 min at which time the reaction was quenched with 15 mL of 1 N aqueous HCl and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was recrystallized from ethyl acetate and hexanes.

Phenylmethyl 3-(2-Chlorophenyl)-3-oxo-2-(2′-pyridyl)-propanoate (1a).[5] Following the general procedure with 2-chlorobenzoyl chloride (0.35 g, 2.0 mmol) afforded **1a**: 69% yield (0.505 g); mp 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 18.38 (s, br, 1H), 8.42 (d, J = 9 Hz, 1H), 7.92 (d, J = 5.67 Hz, 1H), 7.79 (m, 1H), 7.24−6.94 (m, 10H), 4.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 167.8, 155.3, 142.4, 139.7, 135.4, 135.1, 129.9, 129.0, 128.5, 128.1, 127.9, 127.5, 127.2, 126.1, 122.0, 116.8, 96.7, 65.8; IR (neat) 1674, 1373, 1135, 1051 cm^{-1}.

Phenylmethyl 3-(2-Bromophenyl)-3-oxo-2-(2′-pyridyl)-propanoate (1b).[5] Following the general procedure with 2-bromobenzoyl chloride (0.439 g, 2.0 mmol) afforded **1b**: 65% yield (0.533 g); mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 18.4 (s, br, 1H), 8.47 (d, J = 8 Hz, 1H), 7.99 (d, J = 5.5 Hz, 1H), 7.90 (m, 1H), 7.50−6.80 (m, 10H), 4.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 168.0, 155.9, 145.7, 141.0−117.1 (m), 66.3.

Phenylmethyl 3-(2,3-Dichlorophenyl)-3-oxo-2-(2′-pyridyl)propanoate (1c). Following the general procedure with 2,3-dichlorobenzoyl chloride (0.419 g, 2.0 mmol) afforded **1c**:

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56% yield (0.448 g); mp 126−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 18.46 (s, br, 1H), 8.69 (d, J = 8.8 Hz, 1H), 8.13 (s, br, 1H), 8.02 (m, 1H), 7.44−7.13 (m, 9H), 5.02 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 167.8, 155.5, 144.8, 140.2, 135.2, 135.0, 132.8, 129.2, 128.5, 128.3, 128.2, 127.9, 126.9, 125.0, 122.4, 117.1, 96.2, 66.1; IR (neat) 1667, 1545, 1240 cm^{-1}. Anal. Calcd for $C_{21}H_{15}Cl_2NO_3$: C, 62.96; H, 3.78; N, 3.50. Found: C, 62.92; H, 3.65; N, 3.44.

Phenylmethyl 3-(2,4-Dichlorophenyl)-3-oxo-2-(2′-pyridyl)propanoate (1d).[5] Following the general procedure with 2,4-dichlorobenzoyl chloride (0.419 g, 2.0 mmol) afforded **1d**: 75% yield (0.600 g); mp 127−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 18.38 (s, br, 1H), 8.50 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 5.8 Hz, 1H), 7.83 (dd, J = 9.0 Hz, 7.3 Hz, 1H), 7.32−6.59 (m, 9H), 4.86 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 167.8, 155.5, 144.8, 140.2, 135.2, 135.0, 132.8, 129.2, 128.5, 128.3, 128.2, 127.9, 126.9, 125.0, 122.4, 117.1, 96.2, 66.1; IR (neat) 1675, 1625, 1368, 1050 cm^{-1}.

Phenylmethyl 3-(2,6-Dichlorophenyl)-3-oxo-2-(2′-pyridyl)propanoate (1e). Following the general procedure with 2,6-dichlorobenzoyl chloride (0.419 g, 2.0 mmol) afforded **1e**: 53% yield (0.424 g); mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 18.56 (s, br, 1H), 8.76 (d, J = 9.1 Hz, 1H), 8.11 (d, J = 5.8 Hz, 1H), 8.00 (dd, J = 9 Hz, 7.3 Hz, 1H), 7.42−7.18 (m, 8H), 7.02 (dd, J = 8.5 Hz, 7.4 Hz, 1H), 5.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 167.1, 155.4, 141.5, 135.4, 134.7, 130.7, 128.4, 128.1, 128.0, 127.6, 127.2, 122.8, 117.1, 96.6, 65.9; IR (neat) 1664, 1497, 1370, 1272 cm^{-1}. Anal. Calcd for $C_{21}H_{15}Cl_2NO_3$: C, 62.96; H, 3.78; N, 3.50. Found: C, 62.79; H, 3.69; N, 3.46.

Phenylmethyl 3-(2-Chloro-5-(trifluoromethyl)phenyl)-3-oxo-2-(2′-pyridyl) Propanoate (1f). Following the general procedure with 2-chloro-5-(trifluoromethyl)benzoyl chloride (0.486 g, 2.0 mmol) afforded **1f**: 70% yield (0.607 g); mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 18.29 (s, br, 1H), 8.61 (d, J = 9.16 Hz, 1H), 7.97 (d, J = 5.8 Hz, 1H), 7.88 (m, 1H), 7.459 (s, br, 1H), 7.22−7.09 (m, 7H), 6.93 (d, J = 6.8 Hz, 1H), 4.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 167.5, 155.5, 143.6, 140.4, 135.1, 134.9, 133.6, 129.5, 128.7, 128.4, 128.2, 127.9, 125.1, 124.1, 122.6, 118.0, 117.3, 94.4, 66.1; IR (neat) 1664, 1497, 1370, 1272 cm^{-1}. Anal. Calcd for $C_{22}H_{15}ClF_3NO_3$: C, 60.86; H, 3.49; N, 3.23. Found: C, 60.87; H, 3.44; N, 3.25.

Phenylmethyl 3-(2-Bromo-3-nitrophenyl)-3-oxo-2-(2′-pyridyl)propanoate (1g).[5] Following the general procedure with 2-bromo-3-nitrobenzoyl chloride (0.529 g, 2.0 mmol) afforded **1g**: 68% yield (0.621 g); mp 135−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 18.17 (s, br, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 5.6 Hz, 1H), 7.92 (d, J = 4.1 Hz, 1H), 7.44−7.02 (m, 9H), 4.88 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 167.2, 155.3, 149.8, 140.5, 117.3 (m), 66.1; IR (neat) 1680, 1528, 1278 cm^{-1}.

Phenylmethyl 3-(2-Bromo-5-nitrophenyl)-3-oxo-2-(2′-pyridyl)propanoate (1h).[5] Following the general procedure with 2-bromo-5-nitrobenzoyl chloride (0.529 g, 2.0 mmol) afforded **1h**: 60% yield (0.548 g); mp 139−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 18.23 (s, br, 1H), 8.69 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 5.5 Hz, 1H), 7.94−6.94 (m, 10H), 4.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 167.5, 155.7, 146.7, 146.5, 141.0−117.8 (m), 66.4.

Methyl 3-(2,4-Dichlorophenyl)-3-oxo-2-(2′-pyridyl)propanoate (1i). Following the general procedure with 2,4-dichlorobenzoyl chloride (0.419 g, 2.0 mmol) afforded **1i**: 71% yield (0.460 g); mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 18.33 (s, br, 1H), 8.42 (d, J = 9 Hz, 1H), 8.00 (d, J = 5.5 Hz, 1H), 7.88 (m, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.32−7.24 (m, 2H), 7.11 (dd, J = 6.9 Hz, 0.8 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 168.4, 155.3, 141.3, 140.1, 135.1, 133.6, 130.9, 128.9, 128.3, 126.6, 122.2, 117.0, 96.9, 50.8; IR (neat) 1676, 1582, 1485, 1434, 1279, 1062 cm^{-1}. Anal. Calcd for $C_{15}H_{11}Cl_2NO_3$: C, 55.58; H, 3.42; N, 4.32. Found: C, 55.47; H, 3.46; N, 4.28.

Methyl 3-(2,6-Dichlorophenyl)-3-oxo-2-(2′-pyridyl)propanoate (1j). Following the general procedure with 2,6-dichlorobenzoyl chloride (0.419 g, 2.0 mmol) afforded **1j**: 51% yield (0.331 g); mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 18.30 (s, br, 1H), 8.45 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 5.9 Hz, 1H), 7.83 (dt, J = 7.2, 0.6 Hz, 1H), 7.30 (d, J = 7.9 Hz, 2H), 7.14 (t, J = 8.9 Hz, 1H), 7.07 (t, J = 6.0 Hz, 1H), 3.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 167.8, 155.4, 141.7, 140.1, 134.9, 131.0, 128.3, 127.4, 122.8, 117.1, 96.9, 50.8; IR (neat) 1673, 1429, 1375, 1271, 1068, 782 cm^{-1}. Anal. Calcd for $C_{15}H_{11}Cl_2NO_3$: C, 55.58; H, 3.42; N, 4.32. Found: C, 55.32; H, 3.44; N, 4.31.

Phenylmethyl 2-(5-Bromo-2-pyridyl)-3-(2,4-dichlorophenyl)-3-oxopropanoate (1k). A solution of lithium diisopropylamide (0.6 mL, 1.18 mmol) in dry THF (3 mL) was cooled to −78 °C under nitrogen. A solution of benzyl 2-(5-bromo-2-pyridyl)acetate[12] (0.3 g, 0.98 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min at which time a solution of 2,4-dichlorobenzoyl chloride (0.247 g, 1.18 mmol) in dry THF (2 mL) was added slowly. Stirring was continued at 0 °C for an additional 30 min at which time the reaction was quenched with 1 N aqueous HCl (10 mL) and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was recrystallized from ethyl acetate and hexanes to afford **1k**: 85% yield (398 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 18.31 (s, br, 1H), 8.40 (d, J = 9.5 Hz, 1H), 8.37 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 9.3 Hz, 2.4 Hz, 1H), 7.45−7.39 (m, 4H), 7.26 (m, 2H), 7.21 (dd, J = 8.1 Hz, 2.0 Hz, 1H), 7.12 (dd, J = 5.5 Hz, 1.8 Hz, 1H), 5.04 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 166.9, 154.1, 141.7, 139.5, 138.7, 134.7, 134.2, 131.3, 129.0, 128.5, 128.4, 128.1, 128.0, 126.4, 123.3, 112.9, 99.7, 66.5; IR (neat) 1654, 1485, 1352, 1021, 835 cm^{-1}.

6-Oxo-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Benzyl Ester (2a). A solution of **1a** (100 mg, 0.273 mmol) in xylenes (3 mL) was heated to reflux for 20 h in an open upright glass tube. After removal of the solvent and silica gel chromatography (30−80% ethyl acetate/hexanes), the product was recrystallized from ethyl acetate/hexanes to afford **2a**: 45% yield (41 mg); mp 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, J = 6.6 Hz, 1.3 Hz, 1H), 8.53 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 9 Hz, 1H), 7.78−7.26 (m, 9H), 6.74 (m, 1H), 5.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.2, 145.1, 136.2, 136.1, 132.3, 132.0, 128.4, 127.9, 127.6, 127.2, 122.3, 115.2, 112.5, 108.4, 67.0; IR (neat) 1704, 1598, 1210, 1147, 978 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_3 \cdot 0.5H_2O$: C, 74.54; H, 4.78; N, 4.14. Found: C, 74.28; H, 4.52; N, 4.17.

7-Chloro-6-oxo-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Benzyl Ester (2e). A solution of **1e** (198 mg, 0.495 mmol) in xylenes (5 mL) was heated to reflux for 21 h in an open upright glass tube. After removal of the solvent and silica gel chromatography (40−100% ethyl acetate/hexanes), the product was recrystallized from ethyl acetate/hexanes to afford **2e**: 40% yield (73 mg); mp 177−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.7 Hz, 1H), 7.75 (dd, J = 7.9 Hz, 1.8 Hz, 1H), 7.50−7.30 (m, 8H), 7.10 (m, 1H), 6.59 (m, 1H), 5.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 166.9, 144.0, 138.9, 136.1, 135.0, 132.4, 131.1, 130.5, 129.2, 128.5, 128.3, 128.1, 124.9, 121.5, 115.2, 112.4, 110.3, 67.0; IR (neat) 1705, 1581, 1263, 1201, 1116, 992 cm^{-1}. Anal. Calcd for $C_{21}H_{14}ClNO_3$: C, 69.33; H, 3.88; N, 3.85. Found: C, 69.52; H, 3.91; N, 3.82.

9-Chloro-6-oxo-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Benzyl Ester (2d).[5] A solution of **1d** (100 mg, 0.27 mmol) in xylenes (3 mL) was heated to reflux for 2 h in an open upright glass tube. After removal of the solvent and silica gel chromatography (20−80% ethyl acetate/hexanes), the product was recrystallized from ethyl acetate/hexanes to afford **2d**: 82% yield (89 mg); mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (d, J = 7.6 Hz, 1H), 8.7 (s, 1H), 8.32 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.54−6.80 (m, 8H), 5.32 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 167.2, 155.3, 149.8, 149.0, 140.5−117.3 (m), 66.1; IR (neat) 1709, 1587, 1210 cm^{-1}.

10-Chloro-6-oxo-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Benzyl Ester (2c). A solution of **1c (**232 mg, 0.580 mmol) in xylenes (5 mL) was heated to reflux for 9 h in an open upright glass tube. After removal of the solvent and silica gel chromatography (25−60% ethyl acetate/hexanes), the product was recrystallized from ethyl acetate/hexanes to afford

2c: 50% yield (106 mg); mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 5.3 Hz, 1H), 8.51 (dd, J = 7.8 Hz, 1.7 Hz, 1H), 7.91 (d, J = 9.3 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.55−7.52 (m, 3H), 7.39−7.28 (m, 4H), 6.66 (m, 1H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.6, 148.1, 136.5, 135.1, 134.8, 133.5, 129.0, 128.8, 128.3, 128.3, 128.2, 126.6, 123.4, 122.2, 110.3, 67.1; IR (neat) 3057, 1676, 1608, 1582, 1497, 1234, 1155 cm^{-1}. Anal. Calcd for $C_{21}H_{14}ClNO_3 \cdot 0.5H_2O$: C, 67.66; H, 3.79; N, 3.76. Found: C, 67.74; H, 3.72; N, 3.71.

6-Oxo-8-trifluoromethyl-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Benzyl Ester (2f). A solution of **1f** (108 mg, 0.249 mmol) in xylenes (3 mL) was heated to reflux for 4 h in an open upright glass tube. After removal of the solvent and silica gel chromatography (20−80% ethyl acetate/hexanes), the product was recrystallized from ethyl acetate/hexanes to afford **2f**: 69% yield (68 mg); mp 200−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.46 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 9 Hz, 1H), 7.89 (dd, J = 9 Hz, 6.6 Hz, 1H), 7.59−7.53 (m, 3H), 7.40−7.22 (m, 4H), 6.76 (t, J = 6.2 Hz, 1H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 166.7, 145.6, 138.1, 135.9, 132.9, 128.0.6−128.2 (m), 125.6, 124.7, 122.5, 121.9, 116.6, 115.3, 113.2, 109.4, 98.6, 67.2; IR (neat) 1719, 1598, 1491, 1326, 1218, 1118 cm^{-1}. Anal. Calcd for $C_{22}H_{14}F_3NO_3$: C, 66.50; H, 3.56; N, 3.53. Found: C, 66.49; H, 3.59; N, 3.53.

9-Chloro-6-oxo-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Methyl Ester (2i). A solution of **1i** (100 mg, 0.308 mmol) in xylenes (3 mL) was heated to reflux for 2.5 h in an open upright glass tube. After removal of the solvent and silica gel chromatography (20−80% ethyl acetate/hexanes), the product was recrystallized from ethyl acetate/hexanes to afford **2i**: 89% yield (61 mg); mp 235−236 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.6 Hz, 1H), 8.42 (d, J = 7.5 Hz, 1H), 7.99 (d, J = 1.7 Hz, 1H), 7.77 (d, J = 8 Hz, 1H), 7.57 (dd, J = 8.6 Hz, 1.7 Hz, 1H), 7.31 (m, 1H), 6.78 (m, 1H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 167.5, 145.6, 138.6, 136.9, 132.5, 129.4, 128.2, 127.9, 126.9, 122.8, 115.4, 112.9, 108.9, 52.5; IR (neat) 1703, 1572, 1442, 1227, 1155, 998, 747 cm^{-1}.

7-Chloro-6-oxo-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Methyl Ester (2j). A solution of **1j** (95 mg, 0.293 mmol) in xylenes (2 mL) was heated in a long thick glass tube to reflux for 4 h. The tube was open to the atmosphere. For workup, the solvent was removed under reduced pressure, the residue purified by silica gel chromatography (20−60% ethyl acetate/hexanes), and the product recrystallized from ethyl acetate/hexanes to afford **2j**: 55% yield (46 mg); mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.55−7.45 (m, 3H), 7.21 (m, 2H), 6.68 (d, t, J = 7.5, 1.5 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.7, 144.3, 138.9, 135.0, 132.5, 131.1, 130.5, 129.2, 124.9, 121.8, 115.2, 112.6, 110.1, 52.4; IR (neat) 1705, 1581, 1208, 744 cm^{-1}.

2-Bromo-9-chloro-6-oxo-6*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid Benzyl Ester (2k). A solution of **1k** (100 mg, 0.209 mmol) in xylenes (2 mL) was heated in a long thick glass tube to reflux for 2 h with the tube open to the atmosphere. For workup, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (30−50% ethyl acetate/hexanes) to afford **1k**: 54% yield (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 8.6 Hz, 1H), 8.47 (d, J = 1.3 Hz, 1H), 7.93 (d, J = 1.4 Hz, 1H), 7.56−7.54 (m, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.36−7.21 (m, 4H), 5.42 (s, 2H).

4-Hydroxycoumarin Formation (1→3): General Procedure. A solution of phenylmethyl 3-aryl-3-oxo-2(2′-pyridyl)-propanoate **1** (0.2−0.4 mmol) in xylenes (2−5 mL) in a sealed tube was stirred at reflux. After the reaction was complete as indicated by TLC, the mixture was allowed to cool to room temperature. The solid precipitate was collected by filtration and recrystallized from DMSO.

4-Hydroxy-3-(2′-pyridyl)coumarin (3b).[5] Following the general procedure with **1b** (100 mg, 0.30 mmol) in xylenes afforded **3b**: 72% yield (52 mg); mp 270−271 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 17.40 (s, br, 1H), 9.78 (d, J = 9.1 Hz, 1H), 9.61 (d, J = 7.3 Hz, 1H), 8.37 (d, J = 8.85 Hz, 1H), 8.51 (d, J = 6.9 Hz, 1H), 8.09−7.44 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 167.1, 147.5, 136.9, 136.0, 133.3, 132.1, 128.5, 125.9, 125.1, 117.6, 116.5, 99.5; IR (neat) 1695, 1458, 1431, 768 cm^{-1}. Anal. Calcd for $C_{14}H_9NO_3$: C, 70.28; H, 3.80; N, 5.85. Found: C, 69.89; H, 3.83; N, 5.87.

7-Chloro-4-hydroxy-3-(2′-pyridyl)coumarin (3d).[5] Following the general procedure with **1d** (100 mg, 0.27 mmol) in xylenes afforded **3d**: 65% yield (48 mg); mp 277−279 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 17.2 (s, br, 1H), 9.75 (d, J = 9.1 Hz, 1H), 9.53 (d, J = 7.3 Hz, 1H), 8.86 (s, 1H), 8.55 (d, J = 8.7 Hz, 1H), 8.04 (t, J = 7.1 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.2, 166.6, 147.8, 138.4, 137.0, 136.7, 132.3, 128.6, 127.7, 123.9, 122.8, 117.7, 116.3, 99.8; IR (neat) 1675, 1607, 1482, 1422, 798 cm^{-1}.

4-Hydroxy-6-nitro-3-(2′-pyridyl)coumarin (3h).[5] Following the general procedure with **1h** (100 mg, 0.22 mmol) in xylenes afforded **3h**: 96% yield (60 mg); mp 256−259 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 16.7 (s, br, 1H), 9.70 (d, J = 9.3 Hz, 1H), 9.62 (d, J = 7.2 Hz, 1H), 9.07 (d, J = 2.6 Hz, 1H), 8.95 (d, J = 9.5 Hz, 1H), 8.70 (dd, J = 9.5 Hz, 2.6 Hz, 1H), 8.10 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.8, 167.5, 149.2, 147.0, 140.3, 139.5, 134.1, 127.7, 126.6, 123.9, 122.1, 121.5, 118.1, 101.2; IR (BR) 1726, 1668, 1604, 1483, 1341, 1213, 747 cm^{-1}. Anal. Calcd for $C_{14}H_8N_2O_5 \cdot 0.5H_2O$: C, 57.34; H, 3.10; N, 9.56. Found: C, 57.50; H, 2.98; N, 9.40.

4-Hydroxy-8-nitro-3-(2′-pyridyl)coumarin (3g).[5] Following the general procedure with **1g** (100 mg, 0.22 mmol) in xylenes afforded **3g**: 84% yield (52 mg); mp 234−235 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 16.3 (s, br, 1H), 9.50 (d, J = 9.1 Hz, 1H), 8.73 (d, J = 7.9 Hz, 1H), 8.64 (dd, J = 7.9 Hz, J = 0.9 Hz, 1H), 8.35 (t, J = 7.0 Hz, 1H), 8.09−7.3 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 166.8, 149.1, 143.0, 138.5−116.3 (m), 102.0; IR (KBr) 1687, 1524, 1411 cm^{-1}. Anal. Calcd for $C_{14}H_8N_2O_5 \cdot 0.5H_2O$: C, 57.34; H, 3.10; N, 9.56. Found: C, 57.23; H, 2.77; N, 9.38.

4-Hydroxy-6-trifluoromethyl-3-(2′-pyridyl)coumarin (3f). Following the general procedure with **1f** (100 mg, 0.231 mmol) in xylenes afforded **3f**: 88% yield (63 mg); mp 247−249 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 17.03 (s, br, 1H), 9.79 (d, J = 9.1 Hz, 1H), 9.69 (d, J = 7.9 Hz, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.78 (s, 1H), 8.41 (d, J = 9 Hz, 1H), 8.14 (t, J = 6.0 Hz, 1H), 7.52 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 166.8, 148.5, 138.5, 138.2, 132.7, 139.3 (m), 125.9, 125.4 (q, J = 272 Hz), 123.5 (m), 123.2, 120.0, 117.6, 117.1, 100.4; IR (neat) 1653, 1602, 1483, 1321, 1266, 1111, 931, 832, 780, 676 cm^{-1}. Anal. Calcd for $C_{15}H_8F_3NO_3 \cdot 0.5H_2O$: C, 56.97; H, 2.87; N, 4.43. Found: C, 56.60; H, 2.53; N, 4.32.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1k**, **2i**, and **2j** and an ^{1}H NMR spectrum for compound **2k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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