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Synthesis of 7-Aminocoumarins from 7-Hydroxycoumarins via Amide Smiles Rearrangement

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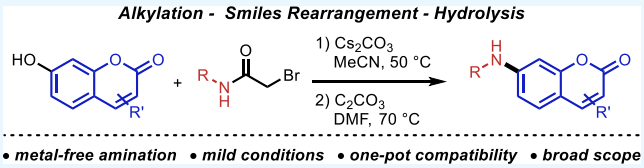
ABSTRACT: N-Substituted 7-aminocoumarins can be synthesized from readily available 7-hydroxycoumarins via alkylation with α-bromoacetamides and subsequent tandem O → N Smiles rearrangement−amide hydrolysis. The key rearrangement sequence proceeds under mild conditions to provide convenient access to various *N*-alkyl and *N*-aryl products in moderate to high yields. The process is operationally simple, inexpensive, transition-metal-free, and can be telescoped into a one-pot process.



INTRODUCTION

The coumarin structural motif continues to attract significant attention owing to its presence in natural product scaffolds,[1] interesting biological activities,[2−4] and useful photophysical properties.[5] In addition to xanthene- and BODIPY-based dyes, coumarins also represent one of the major classes of small molecules amenable to developing fluorescence-based imaging tools for biological and analytical applications.[6] Consequently, modification of these molecules has been heavily investigated, resulting in a large array of valuable luminescent probes and chemical tools.[5] Coumarins bearing nitrogen substitution at the 7-position are highly desirable due to their red-shifted spectral properties, wider pH working range, photostability, and synthetic tunability as compared to their hydroxy analogues.[7] Accordingly, 7-aminocoumarins are commonly employed as central scaffolds in fluorescence applications.[5,8] Construction of these molecules has been historically achieved via Pechmann and related condensation reactions using a suitable aminophenol (Figure 1).[9] While synthetically simple, the requisite harsh conditions and limited substrate availability preclude access to structural diversity. More recently, metal-catalyzed aminations of sulfonates have expanded access to aminocoumarins.[10,11] However, alternative methods that are operationally simple, transition-metal-free, avoid sensitive intermediates, and provide improved chemoselectivity remain highly desirable. We envisioned that a simple amination of inexpensive and readily available 7-hydroxycoumarins would present an attractive route.

The Smiles rearrangement presents a classical and underutilized route for incorporating nitrogen functionality into aromatic systems.[12−14] Bayles and co-workers first detailed the rearrangement of 2-aryloxypropanamides into corresponding anilide products when treated with sodium hydride and heated in DMF or hexamethylphosphoramide.[15,16] Subsequent investigations have expanded this amide-based reactivity for the conversion of phenols into primary or secondary anilides or anilines upon hydrolysis but remain limited by harsh conditions and high temperatures.[17−21] Owing to its

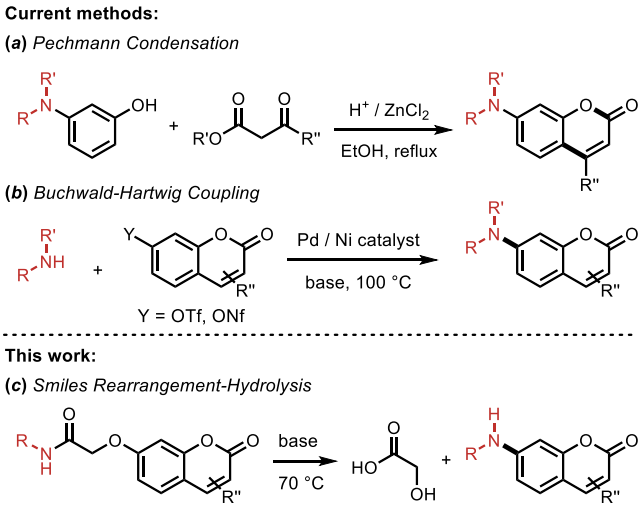


Figure 1. Methods for synthesizing 7-aminocoumarins: (a) Pechmann condensation of aminophenols, (b) Buchwald−Hartwig cross-coupling of sulfonylated hydroxycoumarins, and (c) amination of coumarin ethers via Smiles rearrangement−hydrolysis.

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Scheme 1. Synthesis of Acetamide-Linked Coumarin Substrates

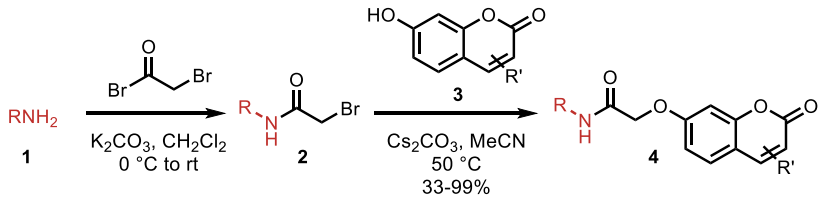
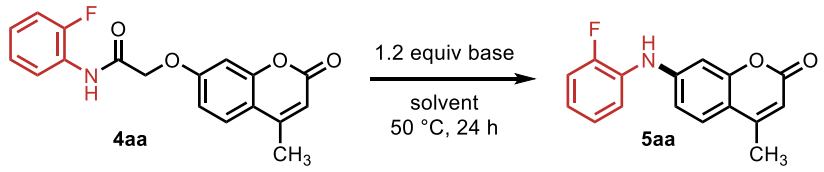


Table 1. Optimization of the Rearrangement−Hydrolysis Reaction[a]



entry[a]	solvent	base	modification	% yield[b]	% conversion[b]
1	THF	KO*t*-Bu		8	20
2	MeCN	KO*t*-Bu		19	23
3	DMA	KO*t*-Bu		68	89
4	DMSO	KO*t*-Bu		50	55
5	DMF	KO*t*-Bu		75	87
6	DMF	K_2CO_3		49	50
7	DMF	Cs_2CO_3		75	85
8	DMF	K_3PO_4		56	62
9	DMF	KOH		72	76
10	DMF	NaH		69	82
11	DMF	Cs_2CO_3	3 Å mol sieves	38	42
12	DMF	Cs_2CO_3	H_2O (1 equiv)	26	30
13	DMF	Cs_2CO_3	2 equiv base	73	79
14	**DMF**	**Cs_2CO_3**	**70 °C**	**84**	**96**
15	DMF	KO*t*-Bu	70 °C	78	88

[a]Reactions were performed on a 40 mg scale. [b]Determined via analysis of the crude reaction via ^{19}F NMR (in DMSO-d_6) using 4,4′-difluorobiphenyl as an internal standard.

electron-withdrawing lactone, we postulated that coumarins may prove amenable to a milder process that might avoid the competitive reactivity of conjugate addition at the 4-position or lactone opening.[5,22,23] We were encouraged by a recent report of a tandem substitution−Smiles rearrangement of aminophenols on 4-bromocoumarins at relatively low temperatures.[24] We therefore sought to determine whether 7-hydroxycoumarins may be efficiently converted to a diverse array of 7-aminocoumarins via an amide-based rearrangement−hydrolysis strategy.

■ RESULTS AND DISCUSSION

To investigate the viability of the proposed rearrangement, several N-substituted acetamide-linked coumarins were prepared as shown in Scheme 1. Acylation of amines with bromoacetyl bromide yielded α-bromoacetamides, and subsequent alkylation with 7-hydroxy-4-methylcoumarin (**3a**) provided a simple, efficient, and chromatography-free route to analytically pure substrates. Previous studies have established significant Thorpe−Ingold effects with respect to linker substitution in Smiles rearrangements.[13,15] Exhaustive efforts to generate the gem-dimethylated substrate via alkylation with 2-methyl-2-bromopropionamide proved unsuccessful.

Initial attempts to induce rearrangement of primary or *N*-alkyl acetamide substrates yielded decomposition and complex mixtures under a range of basic conditions. However, treatment of *N*-aryl substrates with potassium *tert*-butoxide and mild heat interestingly yielded rearranged and hydrolyzed products as indicated by analysis of the crude reaction. Efforts to optimize this tandem process using ^{1}H NMR analysis were complicated by overlapping signals of intermediates, byproducts, and common internal standards. Instead, ^{19}F NMR was utilized as a convenient method for identifying optimal conditions for the tandem rearrangement−hydrolysis process using ortho-fluorinated compound **4aa** as a model substrate (Table 1).

A survey of various polar aprotic solvents indicated DMF as the optimal solvent. The notably limited solubility of the amide substrates is a key factor in the poor yields and conversions when using less polar solvents (e.g., THF, MeCN). Bases with a range of strengths were effective at inducing the rearrangement and hydrolysis, although stronger bases tended to form more complex mixtures and decomposition. Smiles rearrangements employing amide nucleophiles typically employ several equivalents of bases with conjugate acid pK_a values ≥ 16, most commonly NaH or hydroxide. Carbonate bases surprisingly proved suitable for the present transformation, with cesium carbonate providing similar yields as stronger bases and with cleaner reaction profiles. Compatibility with this milder base notably avoids potential safety concerns when heating in DMF or DMSO.[25,26] Addition of 3 Å molecular sieves inhibited the reaction, consistent with involvement of adventitious water in the amide hydrolysis. Additional water or base yielded similar

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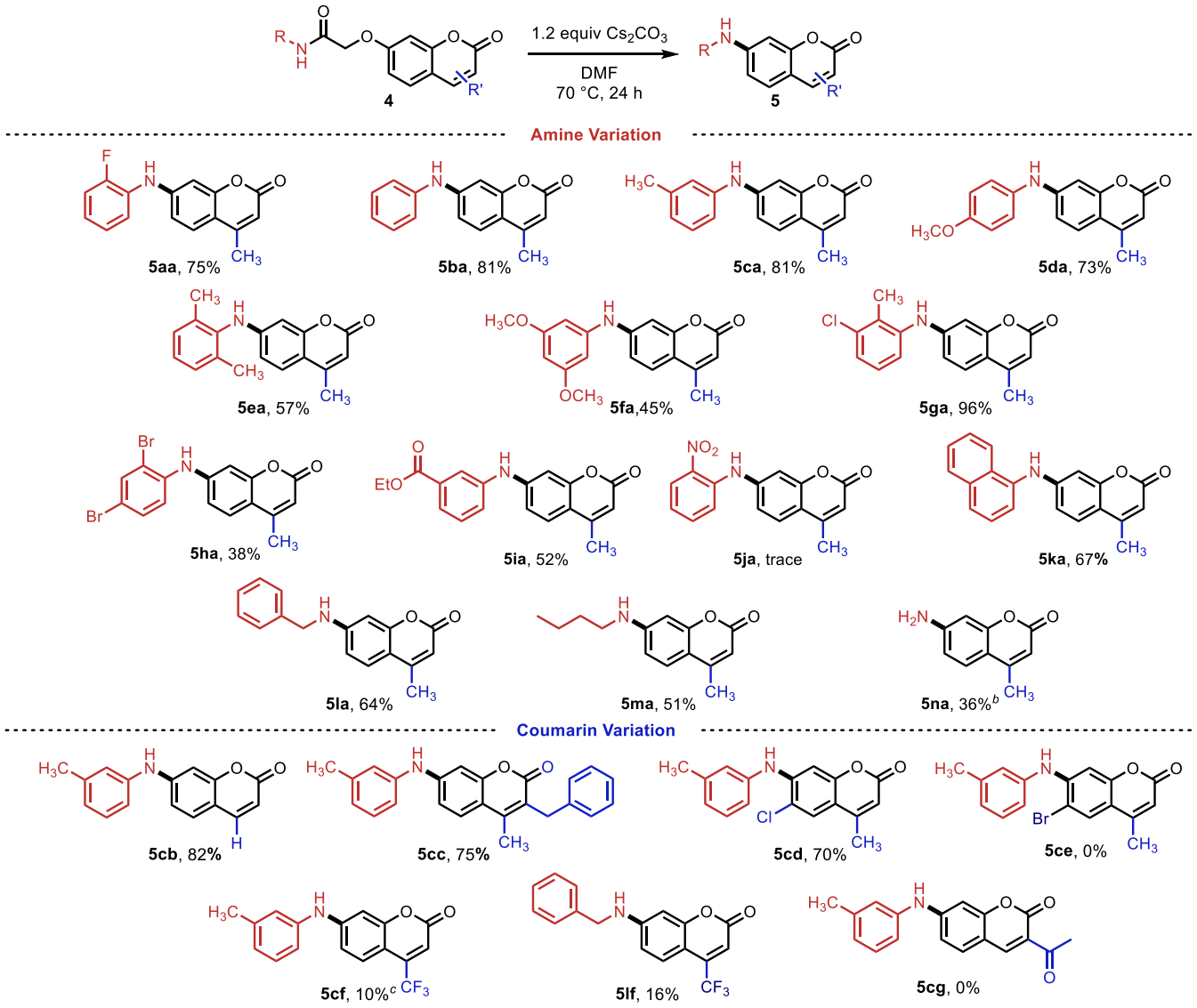
Scheme 2. Substrate Scope of Amines and 7-Hydroxycoumarins in the Tandem Rearrangement−Hydrolysis Reaction[a]



[a]Reactions were performed on a 0.31 mmol scale. Yields refer to isolated yields following column chromatography. [b]Reaction was performed under standard conditions, followed by HCl, EtOH, 90 °C for 5 h. [c]Reaction was performed at 100 °C for 30 h.

deleterious results.[27] Performing the reaction with Cs_2CO_3 at 70 °C improved conversion without significant decomposition.

Having identified optimized conditions, the scope of the rearrangement−hydrolysis reaction was next explored (Scheme 2). With respect to the amide component, substrates comprising neutral or electron-rich anilines underwent successful conversion to product in good yields (**5ba**−**5fa**). Steric hindrance did not noticeably inhibit reactivity and afforded ortho-substituted products in good to moderate yield, including 2,6-dimethyl product **5ea**. Electron-withdrawing moieties including halogens (**5ga** and **ha**) and esters (**5ia**) were tolerated, albeit with more attenuated reactivity, increased decomposition, and more moderate yields. Nitroaniline derivative **4ja**, in addition to the limited solubility, produced only trace amounts of product, even when the reaction was performed at elevated temperatures in DMSO. 1-Naphthyl substrate **4ka** afforded product with good efficiency. The method also proved suitable for alkyl amides, producing *N*-benzyl (**5la**) and *N*-butyl (**5ma**) products in useful yields. In contrast, applying the standard reaction conditions to a primary amide substrate yielded a more complex mixture including only minor amounts of 7-aminocoumarin **5na** and significant amounts of rearranged yet unhydrolyzed intermediate (*vida infra*). A tandem in situ acidic hydrolysis of the intermediate afforded the primary aminocoumarin in moderate yield.

Structural variation on the coumarin skeleton was also explored. Coumarins with substitution at the 4-position are commonly employed in order to attenuate known vinylogous reactivity. Umbelliferone derivative **4cb**, which is unsubstituted at the 4-position, successfully afforded product **5cb** without any observed competing reactivity. 4-Methylcoumarins bearing additional substitution at the 3- or 6-position similarly provided the desired products (**5cc**-**5cd**) in good yields. Notably, 6-chloro derivative **4cd** avoided competitive *ortho* S_NAr reactivity of the amide, which has been observed in related processes to afford benzoxazinone derivatives.[17] In contrast, bromo analogue **4ce** failed to react even under

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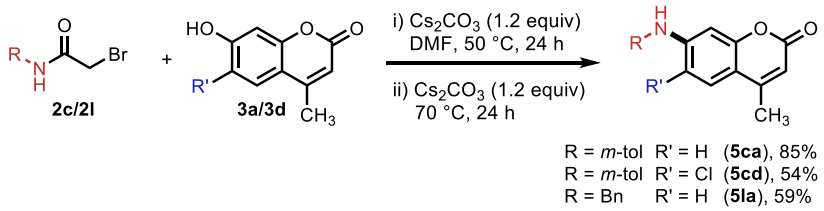
Scheme 3. One-Pot Alkylation−Rearrangement−Hydrolysis Sequence



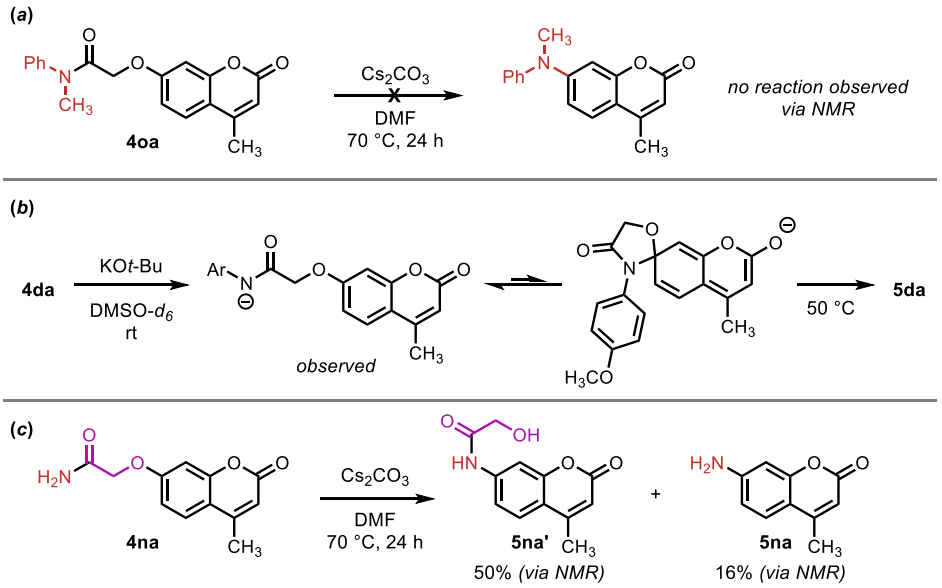


Figure 2. Mechanistic studies: (a) treatment of tertiary amide **4oa** with standard reaction conditions, (b) stepwise analysis of the rearrangement−hydrolysis sequence of **4da** via NMR monitoring, and (c) formation of the unhydrolyzed intermediate when applying standard reaction conditions to primary amide **4na.**

significantly higher temperatures, potentially arising from limited solubility and increased steric hindrance in proximity to the desired ipso attack. Owing to stabilization of the key Meisenheimer intermediate, electronically deficient arenes are generally exceptional substrates in processes invoking Smiles rearrangements. Surprisingly, 4-trifluoromethylcoumarins bearing either *N*-aryl (**4cf**) or *N*-alkyl amides (**4lf**) displayed attenuated reactivity, affording poorer yields and increased decomposition under the reaction conditions. A 3-acetyl-substituted substrate rapidly formed a complex mixture without evidence of the desired product **5cg**, potentially due to undesired reactivity at the doubly activated and unhindered 4-position.

The alkylation, rearrangement, and hydrolysis steps occur under reasonably similar basic conditions with heating, inviting the possibility of a tandem procedure for providing direct conversion of the hydroxycoumarin to the amine-functionalized product.[18] Gratifyingly, treatment of coumarin **3a** and bromoacetamide **2c** with the standard rearrangement conditions and 2.4 equiv of Cs_2CO_3 provided the desired aminocoumarin product **5ca** with only slightly lower efficiency compared to the stepwise procedure (see the Supporting Information). Alternatively, a one-pot process in which sequential alkylation and rearrangement−hydrolysis are controlled via temperature and base addition improved the isolated yield to 85% (Scheme 3). Application of this strategy to other substrates produced aminocoumarins **5cd** and **5la** in only slightly depressed yields as compared to the one-step procedure, indicating compatibility with variation in amine and hydroxycoumarin precursors. This procedure presents a convenient and direct amination of the hydroxyl unit without a separate prefunctionalization step.

Experiments were performed to provide additional information on the nature of the reaction sequence (Figure 2). Exposure of tertiary amide **4oa** to standard rearrangement conditions did not effect any reaction, and only the starting material was indicated by NMR analysis of the crude reaction mixture (Figure 2a). When monitored by ^{1}H NMR, treatment of substrate **4da** with 1.5 equiv of potassium *tert*-butoxide at room temperature was accompanied by the appearance of a single intermediate, exhibiting significant upfield shifts to hydrogens associated with the aniline ring and methylene linker as well as loss of the amide hydrogen signal (Figure 2b, also see the Supporting Information). Slow conversion of this ostensibly deprotonated intermediate to product **5da** was observed by heating at 50 °C. Interestingly, primary amide **4na** formed significant amounts of the direct rearrangement compound **5na′** along with minor amounts of the subsequent hydrolysis product **5na** (Figure 2c).[28] Hydrolysis of intermediate **5na′** may be impeded by favorable deprotonation of the amide proton affording the anion and decreased reactivity at the amide carbonyl. Indeed, attempts to saponify this intermediate under forcing conditions with hydroxide proved ineffective. Such a pathway is unavailable for secondary substrates, as the intermediate contains no acidic N−H, and their comparably facile amide hydrolysis may also be explained by the extended conjugation of the nitrogen into the coumarin moiety. Taken together, a mechanism invoking a canonical

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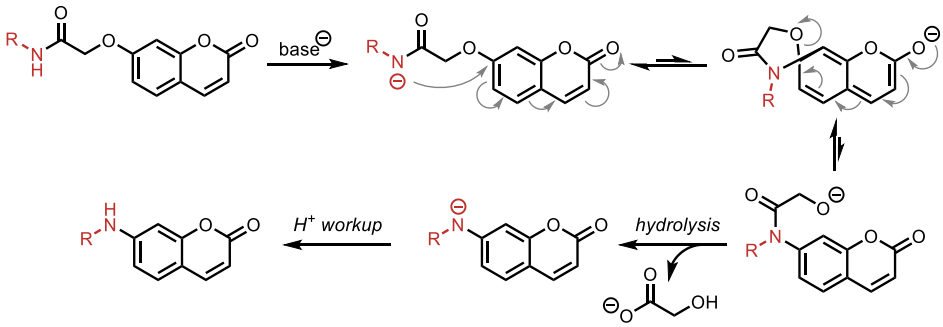
Scheme 4. Proposed Mechanism



base-mediated Smiles rearrangement and subsequent amide hydrolysis (Scheme 4) is consistent with the abovementioned observations and is proposed for the present amination reaction.[16,29]

In summary, a method for preparing *N*-aryl or *N*-alkyl 7-aminocoumarins from readily available hydroxylated precursors has been developed that exploits a key O → N Smiles rearrangement. This process is operationally simple, employs inexpensive reagents, and avoids hydrolytically sensitive intermediates typically required with metal-catalyzed amination methods. Notably, the alkylation−rearrangement−hydrolysis sequence may be telescoped into a direct, one-pot amination from the respective α-bromoacetamide. Substrates containing an array of functionalities are tolerated, including electron-deficient anilines and halogens, providing access to unique chemical space that may prove challenging by existing methods. Efforts to extend this strategy to explore new xanthene fluorophores as well as ratiometric imaging applications are ongoing.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out in flame-dried glassware under argon. Solvents were purchased as HPLC-grade from Sigma-Aldrich and used without further purification. Umbelliferone was purchased from Tokyo Chemical Industry Company. Cesium carbonate was purchased from Alfa Aesar. All other reagents were purchased from Oakwood Chemical. ^{1}H NMR and ^{13}C NMR data were collected in $CDCl_3$ (Sigma-Aldrich) or DMSO-d_6 (Oakwood Chemical) at 27 °C on a 300 MHz Bruker AVANCE III HD spectrometer. Chemical shifts (δ) are reported in parts per million relative to residual solvent signals of $CDCl_3$ (7.27 ppm for ^{1}H and 77.16 ppm for ^{13}C) or DMSO-d_6 (2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C). Splitting patterns: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dq, doublet of quartets; bs, broad singlet; bd, broad doublet. Thin-layer chromatography was performed on Baker-flex silica gel IB-F TLC plates (J.T. Baker), and flash column chromatography was performed using SiliaFlash P60 silica gel (SiliCycle). α-Bromoacetamides **2** are known compounds and were synthesized according to a literature procedure.[30] Hydroxycoumarins **3c**,[31] **3d**,[32] **3e**,[33] and **3g**[34] were synthesized according to literature procedures.

General Procedure 1: Synthesis of *O*-Alkylated Coumarins. A round-bottom flask was charged with hydroxycoumarin (1 equiv) and Cs_2CO_3 (1.2 equiv). Acetonitrile (0.15 M) was added, followed by the respective α-bromoacetamide (1.2 equiv), and the resulting slurry was stirred in a 50 °C oil bath for 16 h. The solvent was removed in vacuo, and the resulting residue was washed with CH_2Cl_2 or Et_2O and then H_2O to provide the desired *O*-alkylated coumarin product.

General Procedure 2: Synthesis of Aminocoumarins via Rearrangement−Hydrolysis. A solution of alkylated coumarin (0.31 mmol) in DMF (3.1 mL, 0.1 M) was prepared under argon in a dry round-bottom flask. After adding Cs_2CO_3 (121 mg, 0.37 mmol), the resulting slurry was stirred vigorously for 24 h in a 70 °C oil bath. The mixture was cooled, the solvent was removed in vacuo, and the resulting solid was washed with 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over sodium sulfate, concentrated in vacuo, and purified via flash column chromatography to afford the title compound.

*N-(2-Fluorophenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (**4aa**).* Synthesized according to General Procedure 1 on a 8.62 mmol scale to afford the title compound as a white powder (1.72 g, 73%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.98 (br s, 1H), 7.82−7.75 (m, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.32−7.14 (m, 3H), 7.08−6.99 (m, 2H), 6.23 (d, J = 1.2 Hz, 1H), 4.91 (s, 2H), 2.40 (d, J = 1.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.3, 160.8, 160.1, 154.5, 154.2 (d, J = 244.9 Hz), 153.4, 126.5, 125.9 (d, J = 7.9 Hz), 125.6 (d, J = 11.4 Hz), 124.8, 124.4 (d, J = 3.8 Hz), 115.6 (d, J = 19.3 Hz), 113.6, 112.4, 111.4, 101.6, 67.1, 18.1. FTIR (ATR, cm^{-1}) 3350, 3075, 1707, 1688, 1613, 1526, 1389, 1295. HRMS (EI) m/z: [M$^+$] calcd for $C_{18}H_{14}FNO_4$, 327.0907; found, 327.0900.

*2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)-N-phenylacetamide (**4ba**).* Synthesized according to General Procedure 1 on a 1.2 mmol (211 mg) scale to afford the title compound as a light pink solid (342 mg, 96%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.14 (s, 1H), 7.73, (d, J = 8.7 Hz, 1H), 7.63, (d, J = 7.7 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.12−7.01 (m, 3H), 6.23 (d, J = 1.3 Hz, 1H), 4.85 (s, 2H), 2.41 (d, J = 1.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.8, 160.9, 160.0, 154.6, 153.4, 138.3, 128.8, 126.6, 123.8, 119.7, 113.7, 112.4, 111.4, 101.7, 67.3, 18.1. FTIR (ATR, cm^{-1}) 3364, 1700, 1673, 1626, 1598, 1536. HRMS (EI) m/z: [M$^+$] calcd for $C_{18}H_{15}NO_4$, 309.1001; found, 309.0994.

*2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(m-tolyl)-acetamide (**4ca**).* Synthesized according to General Procedure 1 on a 1.13 mmol scale to afford the title compound as a white powder (235 mg, 64%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.07 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.48 (s, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.06 (dd, J = 8.7, 2.5 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.24 (d, J = 1.2 Hz, 1H), 4.84 (s, 2H), 2.41 (d, J = 1.2 Hz, 3H), 2.29 (s, 3H) ^{13}C{H} NMR (75 MHz, DMSO-d_6,

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ppm): δ 165.8, 160.8, 160.1, 154.5, 153.3, 138.2, 138.0, 128.6, 126.5, 124.4, 120.2, 116.9, 113.7, 112.4, 111.4, 101.7, 67.3, 21.2, 18.1. FTIR (ATR, cm^{-1}) 3355, 1679, 1612, 1597, 1540, 1293. HRMS (EI) *m/z*: [M^+] calcd for $C_{19}H_{17}NO_4$, 323.1158; found, 323.1151.

*N-(4-Methoxyphenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (**4da**).* Synthesized according to General Procedure 1 on a 1.70 mmol scale to afford the title compound as a white powder (276 mg, 75%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.00 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.58−7.49 (m, 2H), 7.09−7.00 (m, 2H), 6.94−6.86 (m, 2H), 6.23 (d, *J* = 1.2 Hz, 1H), 4.81 (s, 2H), 3.73 (s, 3H), 2.41 (d, *J* = 1.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.3, 160.8, 160.0, 155.6, 154.5, 153.3, 131.3, 126.5, 121.3, 113.9, 113.6, 112.4, 111.5, 101.7, 67.3, 55.2, 18.1. FTIR (ATR, cm^{-1}) 3362, 1691, 1674, 1615, 1596, 1540, 1297. HRMS (EI) *m/z*: [M^+] calcd for $C_{19}H_{17}NO_5$, 339.1107; found, 339.1104.

*N-(2,6-Dimethylphenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (**4ea**).* Synthesized according to General Procedure 1 on a 1.11 mmol scale to afford the title compound as a white powder (247 mg, 66%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.58 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.14−7.03 (m, 5H), 6.24 (d, *J* = 1.1 Hz, 1H), 4.88 (s, 2H), 2.41 (d, *J* = 1.1 Hz, 3H), 2.13 (s, 6H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.8, 160.8, 160.1, 154.5, 153.4, 135.3, 134.3, 127.7, 126.7, 126.5, 113.7, 112.6, 111.5, 101.8, 67.1, 18.1, 18.0. FTIR (ATR, cm^{-1}) 3334, 2914, 1710, 1667, 1623, 1501, 1289. HRMS (EI) *m/z*: [M^+] calcd for $C_{20}H_{19}NO_4$, 337.1314; found, 337.1305.

*N-(3,5-Dimethoxyphenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (**4fa**).* Synthesized according to General Procedure 1 on a 1.39 mmol scale to afford the title compound as a white powder (324 mg, 63%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.09 (s, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.09−7.01 (m, 2H), 6.90 (d, *J* = 2.3 Hz, 2H), 6.26 (t, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 1.2 Hz, 1H), 4.83 (s, 2H), 3.72 (s, 6H), 2.41 (d, *J* = 1.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.9, 160.8, 160.5, 160.1, 154.5, 153.3, 140.0, 126.5, 113.7, 112.4, 111.5, 101.7, 97.9, 95.7, 67.3, 55.1, 18.1. FTIR (ATR, cm^{-1}) 3346, 1700, 1680, 1611, 1543, 1294. HRMS (EI) *m/z*: [M^+] calcd for $C_{20}H_{19}NO_6$, 369.1212; found, 369.1208.

*N-(3-Chloro-2-methylphenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (**4ga**).* Synthesized according to General Procedure 1 on a 1.44 mmol scale to afford the title compound as a white solid (387 mg, 90%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.85 (s, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.37−7.30 (m, 2H), 7.27−7.18 (m, 1H), 7.11−7.02 (m, 2H), 6.24 (d, *J* = 1.2 Hz, 1H), 4.90 (s, 2H), 2.41 (d, *J* = 1.2 Hz, 3H), 2.22 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.3, 160.8, 160.1, 154.6, 153.3, 137.1, 133.7, 131.1, 126.9, 126.6 (2 resonances based on intensity), 124.9, 113.7, 112.4, 111.5, 101.7, 67.2, 18.1, 15.0. FTIR (ATR, cm^{-1}) 3350, 1695, 1613, 1530, 1393, 1282. HRMS (EI) *m/z*: [M^+] calcd for $C_{19}H_{16}{}^{35}ClNO_4$, 357.0768; found, 357.0769.

*N-(2,4-Dibromophenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (**4ha**).* Synthesized according to General Procedure 1 on a 1.42 mmol scale to afford the title compound as a white solid (375 mg, 57%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.73 (s, 1H), 7.96 (d, *J* = 2.2 Hz, 1H), 7.78−7.71 (m, 2H), 7.62 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.09 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.08 (s, 1H), 6.26 (d, *J* = 1.2 Hz, 1H), 4.92 (s, 2H), 2.42 (d, *J* = 1.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.3, 160.4, 160.0, 154.5, 153.4, 135.0, 134.6, 131.2, 127.4, 126.6, 118.5, 118.2, 113.8, 112.5, 111.6, 101.9, 67.2, 18.1. FTIR (ATR, cm^{-1}) 3370, 1717, 1703, 1615, 1568, 1506, 1388. HRMS (EI) *m/z*: [M^+] calcd for $C_{18}H_{13}{}^{79}Br_2NO_4$, 464.9211; found, 464.9218.

*Ethyl 3-(2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)-acetamido)benzoate (**4ia**).* Synthesized according to General Procedure 1 on a 1.20 mmol scale to afford the title compound as a white solid (453 mg, 99%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.29 (t, *J* = 1.8 Hz, 1H), 7.90 (m, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.09−7.01 (m, 2H), 6.23 (d, *J* = 1.2 Hz, 1H), 4.87 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.40 (d, *J* = 1.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.3, 165.5, 160.9, 160.1, 154.5, 153.4, 139.0, 130.5, 129.3, 126.6, 124.2, 124.2, 120.2, 113.7, 112.4, 111.5, 101.8, 67.3, 60.9, 18.1, 14.2. FTIR (ATR, cm^{-1}) 3344, 1720, 1688, 1625, 1544, 1283. HRMS (EI) *m/z*: [M^+] calcd for $C_{21}H_{19}NO_6$, 381.1212; found, 381.1212.

*2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(2-nitrophenyl)acetamide (**4ja**).* Synthesized according to General Procedure 1 on a 1.20 mmol scale to afford the title compound as a tan solid (414 mg, 97%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.83 (br s, 1H), 8.08−8.02 (m, 2H), 7.79−7.71 (m, 2H), 7.40−7.33 (m, 1H), 7.11−7.05 (m, 2H), 6.25 (d, *J* = 1.2 Hz, 1H), 4.90 (s, 2H), 2.41 (d, *J* = 1.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.7, 160.3, 160.0, 154.6, 153.3, 140.7, 134.7, 132.2, 126.7, 125.2, 124.8, 124.3, 113.9, 112.6, 111.7, 101.9, 67.4, 18.1 FTIR (ATR, cm^{-1}) 3305, 1708, 1615, 1583, 1503, 1427, 1282. HRMS (EI) *m/z*: [M^+] calcd for $C_{18}H_{14}N_2O_6$, 354.0852; found, 354.0850.

*2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(naphthalen-1-yl)acetamide (**4ka**).* Synthesized according to General Procedure 1 on a 1.20 mmol scale to afford the title compound as a white solid (398 mg, 92%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.22 (s, 1H), 8.07−8.00 (m, 1H), 7.99−7.92 (m, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.66 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.59−7.48 (m, 3H), 7.17−7.08 (m, 2H), 6.24 (d, *J* = 1.2 Hz, 1H), 5.03 (s, 2H), 2.42 (d, *J* = 1.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.8, 160.9, 160.1, 154.6, 153.4, 133.7, 132.7, 128.1 (2 resonances based on intensity), 126.6, 126.1, 126.0, 125.9, 125.6, 122.8, 122.4, 113.7, 112.5, 111.5, 101.8, 67.3, 18.1. FTIR (ATR, cm^{-1}) 3239, 3210, 1721, 1667, 1615, 1542, 1389, 1260. HRMS (EI) *m/z*: [M^+] calcd for $C_{22}H_{17}NO_4$, 359.1158; found, 359.1155.

*N-Benzyl-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-acetamide (**4la**).* Synthesized according to General Procedure 1 on a 1.70 mmol scale to afford the title compound as a white solid (491 mg, 89%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.74 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.36−7.18 (m, 5H), 7.03 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.23 (d, *J* = 1.2 Hz, 1H), 4.70 (s, 2H), 4.35 (s, 2H), 2.40 (d, *J* = 1.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 167.1, 160.7, 160.1, 154.5, 153.4, 139.2, 128.2, 127.3, 126.8, 126.5, 113.6, 112.6, 111.5, 101.7, 67.2, 41.9, 18.2. FTIR (ATR, cm^{-1}) 3370, 1713, 1667, 1624, 1539, 1273. HRMS (EI) *m/z*: [M^+] calcd for $C_{19}H_{17}NO_4$, 323.1158; found, 323.1159.

*N-Butyl-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-acetamide (**4ma**).* Synthesized according to General Procedure 1 on a 2.84 mmol scale. After washing the crude solid with water and Et_2O, the solid was dissolved in CH_2Cl_2 (30

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mL), washed with sat aq $NaHCO_3$ (2 × 20 mL) and water (20 mL), dried over sodium sulfate, filtered, and concentrated to afford the title compound and small amounts of unreacted **3a** (~7% by ^{1}H NMR) as a white solid (272 mg, 33%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.13 (t, J = 5.6 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.00 (dd, J = 8.8, 2.6 Hz, 1H), 6.95 (d, J = 2.5 Hz, 1H), 6.22 (d, J = 1.2 Hz, 1H), 4.60 (s, 2H), 3.13 (q, J = 6.5 Hz, 2H), 2.40 (d, J = 1.2 Hz, 3H), 1.48−1.35 (m, 2H), 1.33−1.18 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.7, 160.7, 160.0, 154.5, 153.4, 126.5, 113.6, 112.5, 111.4, 101.7, 67.2, 38.0, 31.2, 19.5, 18.1, 13.6. FTIR (ATR, cm^{-1}) 3380, 2926, 1720, 1659, 1627, 1550, 1390. HRMS (EI) m/z: [M$^+$] calcd for $C_{16}H_{19}NO_4$, 289.1314; found, 289.1311.

*2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (**4na**).* Synthesized according to General Procedure 1 on a 1.42 mmol scale using K_2CO_3 (235 mg, 1.2 equiv) in place of Cs_2CO_3 to afford the title compound as a white solid (269 mg, 81%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 7.70 (d, J = 8.8 Hz, 1H), 7.61 (br s, 1H), 7.43 (br s, 1H), 7.00 (dd, J = 8.8, 2.5 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.22 (d, J = 1.1 Hz, 1H), 4.56 (s, 2H), 2.39 (d, J = 1.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 169.2, 160.8, 160.1, 154.5, 153.4, 126.5, 113.6, 112.5, 111.4, 101.7, 66.9, 18.1. FTIR (ATR, cm^{-1}) 3440, 3178, 1736, 1691, 1619, 1390, 1294. HRMS (EI) m/z: [M$^+$] calcd for $C_{12}H_{11}NO_4$, 233.0688; found, 233.0690.

*2-((2-Oxo-2H-chromen-7-yl)oxy)-N-(m-tolyl)acetamide (**4cb**).* Synthesized according to General Procedure 1 on a 0.925 mmol scale to afford the title compound as a tan solid (151 mg, 53%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.06 (s, 1H), 8.01 (d, J = 9.6 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.48 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.05 (dd, J = 7.8, 2.5 Hz, 1H), 7.03 (s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 4.84 (s, 2H), 2.29 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.7, 161.0, 160.8, 155.2, 144.2, 138.2, 138.0, 129.5, 128.6, 124.4., 120.2, 116.9, 112.8, 112.8, 112.7, 101.6, 67.3, 21.1. FTIR (ATR, cm^{-1}) 3367, 1726, 1686, 1612, 1543, 1490, 1290. HRMS (EI) m/z: [M$^+$] calcd for $C_{18}H_{15}NO_4$, 309.1001; found, 309.1007.

*2-((3-Benzyl-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(m-tolyl)acetamide (**4cc**).* Synthesized according to General Procedure 1 on a 1.35 mmol scale to afford the title compound as a white powder (526 mg, 94%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.08 (br s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.48 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.31−7.14 (m, 6H), 7.09−7.01 (m, 2H), 6.91 (d, J = 7.4 Hz, 1H), 4.84 (s, 2H), 3.96 (s, 2H), 2.44 (s, 3H), 2.29 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.8, 161.2, 160.2, 153.2, 148.3, 139.3, 138.4, 138.0, 128.6, 128.4, 128.0, 126.7, 126.1, 124.4, 121.3, 120.2, 116.9, 114.1, 112.4, 101.4, 67.3, 32.2, 21.1, 15.2. FTIR (ATR, cm^{-1}) 3296, 1708, 1666, 1590, 1557, 1386, 1280. HRMS (EI) m/z: [M$^+$] calcd for $C_{26}H_{23}NO_4$, 413.1627; found, 413.1628.

*2-((6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(m-tolyl)acetamide (**4cd**).* Synthesized according to General Procedure 1 on a 1.20 mmol scale to afford the title compound as a white powder (359 mg, 84%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.12 (s, 1H), 7.87 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.18 (s, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.29 (d, J = 1.2 Hz, 1H), 4.98 (s, 2H), 2.41 (d, J = 1.2 Hz, 3H), 2.28 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.1, 159.6, 156.0, 153.0, 152.7, 138.3, 139.1, 128.7, 126.1, 124.4, 120.0, 117.8, 116.5, 114.1, 112.3, 101.9, 67.8, 21.2, 18.1. FTIR (ATR, cm^{-1}) 3399, 1715, 1692, 1608, 1547, 1489, 1388, 1277. HRMS (EI) m/z: [M$^+$] calcd for $C_{19}H_{16}{}^{35}ClNO_4$, 357.0768; found, 357.0778.

*2-((6-Bromo-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(m-tolyl)acetamide (**4ce**).* Synthesized according to General Procedure 1 on a 1.42 mmol scale to afford the title compound as a white powder (387 mg, 68%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.10 (s, 1H), 8.00 (s, 1H), 7.46 (s, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.16 (s, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.29 (d, J = 1.2 Hz, 1H), 4.97 (s, 2H), 2.42 (d, J = 1.2 Hz, 3H), 2.29 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.1, 159.6, 156.8, 153.6, 152.6, 138.2, 138.1, 129.0, 128.7, 124.4, 119.8, 116.5, 114.7, 112.2, 106.8, 101.7, 68.0, 21.1, 18.1. FTIR (ATR, cm^{-1}) 3395, 1717, 1692, 1602, 1547, 1489, 1361, 1273. HRMS (EI) m/z: [M$^+$] calcd for $C_{19}H_{16}{}^{79}BrNO_4$, 401.0263; found, 401.0269.

*2-((2-Oxo-4-(trifluoromethyl)-2H-chromen-7-yl)oxy)-N-(m-tolyl)acetamide (**4cf**).* Synthesized according to General Procedure 1 on a 1.20 mmol scale to afford the title compound as a white powder (394 mg, 87%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.09 (s, 1H), 7.67 (dd, J = 8.8, 1.9 Hz, 1H), 7.46 (s, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.24−7.12 (m, 3H), 6.91 (d, J = 7.5 Hz, 1H), 6.87 (s, 1H), 4.89 (s, 2H), 2.28 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.5, 161.7, 158.7, 155.6, 139.4 (q, J = 32.5 Hz), 138.2, 138.0, 128.6, 125.9, 124.5, 121.7 (q, J = 275.7 Hz), 120.1, 116.8, 113.6, 113.6, 106.9, 102.6, 67.3, 21.1. FTIR (ATR, cm^{-1}) 3363, 1731, 1671, 1614, 1547, 1280. HRMS (EI) m/z: [M$^+$] calcd for $C_{19}H_{14}F_3NO_4$, 377.0875; found, 377.0871.

*N-Benzyl-2-((2-oxo-4-(trifluoromethyl)-2H-chromen-7-yl)-oxy)acetamide (**4lf**).* Synthesized according to General Procedure 1 on a 1.20 mmol scale to afford the title compound as a white powder (405 mg, 89%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.74 (t, J = 6.1 Hz, 1H), 7.66 (dd, J = 9.5, 2.0 Hz, 1H), 7.34−7.19 (m, 5H), 7.14 (s, 1H), 7.12 (dd, J = 7.7, 2.6 Hz, 1H), 6.88 (s, 1H), 4.75 (s, 2H), 4.35 (d, J = 6.1 Hz, 2H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 166.8, 161.5, 158.6, 155.6, 139.3 (q, J = 32.1 Hz), 139.1, 128.2, 127.2, 126.8, 125.9, 121.7 (q, J = 274.6 Hz), 113.8, 113.6 (q, J = 5.9 Hz), 106.9, 102.6, 67.2, 41.9. FTIR (ATR, cm^{-1}) 3357, 1730, 1671, 1615, 1539, 1282. HRMS (EI) m/z: [M$^+$] calcd for $C_{19}H_{14}F_3NO_4$, 377.0875; found, 377.0875.

*2-((3-Acetyl-2-oxo-2H-chromen-7-yl)oxy)-N-(m-tolyl)-acetamide (**4cg**).* Synthesized according to General Procedure 2 on a 1.34 mmol scale to afford the title compound as a pale-yellow solid (386 mg, 85%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.09 (s, 1H), 8.65 (s, 1H), 7.94−7.89 (m, 1H), 7.46 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.14−7.08 (m, 2H), 6.91 (d, J = 7.5 Hz, 1H), 4.89 (s, 2H), 2.56 (s, 3H), 2.28 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 194.8, 165.5, 163.3, 158.8, 156.8, 147.5, 138.2, 138.0, 132.2, 128.6, 124.5, 120.8, 120.2, 116.9, 113.7, 112.3, 101.2, 67.4, 30.1, 21.2. FTIR (ATR, cm^{-1}) 3282, 1735, 1673, 1618, 1538, 1213. HRMS (EI) m/z: [M$^+$] calcd for $C_{20}H_{17}NO_5$, 351.1107; found, 351.1103.

*N-Methyl-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-phenylacetamide (**4oa**).* Synthesized according to General Procedure 2 on a 3.65 mmol scale to afford the title compound as a white solid (750 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.56−7.39 (m, 4H), 7.32−7.27 (m, 2H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.14 (m, 1H), 4.47 (s, 2H), 3.34 (s, 3H), 2.39 (d, J = 1.2 Hz, 3H). ^{13}C{H} NMR

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(75 MHz, $CDCl_3$, ppm): δ 166.6, 161.3, 161.1, 155.1, 152.6, 142.0, 130.4, 129.0, 127.1, 125.7, 114.2, 113.1, 112.3, 101.4, 66.3, 37.7, 18.8. FTIR (ATR, cm^{-1}) 1724, 1686, 1616, 1596, 1393, 1275. HRMS (EI) *m/z*: [M^+] calcd for $C_{19}H_{17}NO_4$, 323.1158; found, 323.1158.

*7-((2-Fluorophenyl)amino)-4-methyl-2H-chromen-2-one (**5aa**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 20%−30% EtOAc/Hex provided the title compound as a tan solid (61.4 mg, 75%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.69 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.42 (td, *J* = 8.2, 1.8 Hz, 1H), 7.35−7.26 (m, 1H), 7.24−7.10 (m, 2H), 6.90 (ddd, *J* = 8.7, 2.3, 0.7 Hz, 1H), 6.71−6.68 (m, 1H), 6.07 (d, *J* = 1.1 Hz, 1H), 2.36 (d, *J* = 1.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 160.3, 155.0 (d, *J* = 243.9 Hz), 154.9, 153.4, 148.2, 128.4 (d, *J* = 11.6 Hz), 126.3, 125.0 (d, *J* = 3.7 Hz), 124.6 (d, *J* = 7.7 Hz), 123.5 (d, *J* = 2.7 Hz), 116.4 (d, *J* = 19.4 Hz), 111.9, 111.5, 109.6, 100.2, 18.0. FTIR (ATR, cm^{-1}) 3316, 3064, 1691, 1605, 1485. HRMS (EI) *m/z*: [M^+] calcd for $C_{16}H_{12}FNO_2$, 269.0852; found, 269.0854.

*4-Methyl-7-(phenylamino)-2H-chromen-2-one (**5ba**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 15%−25% EtOAc/Hex provided the title compound as a yellow-orange solid (62.9 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.44 (d, *J* = 8.6 Hz, 1H), 7.40−7.32 (m, 2H), 7.23−7.17 (m, 2H), 7.14−7.07 (m, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.15 (br s, 1H), 6.07 (d, *J* = 1.1 Hz, 1H), 2.38 (d, *J* = 1.2 Hz, 3H). Spectral data are in agreement with literature values.[35]

*4-Methyl-7-(m-tolylamino)-2H-chromen-2-one (**5ca**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 15%−30% EtOAc/Hex provided the title compound as a pale-yellow solid (66.5 mg, 81%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.81 (br s, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.25−7.20 (m, 1H), 7.02−6.95 (m, 3H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.85−6.82 (m, 1H), 6.05 (d, *J* = 1.2 Hz, 1H), 2.35 (d, *J* = 2.1 Hz, 3H), 2.97 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm) 160.4, 155.0, 153.4, 148.0, 141.0, 138.8, 129.2, 126.4, 123.0, 120.0, 116.7, 112.2, 111.3, 109.3, 99.9, 21.1, 18.0. FTIR (ATR, cm^{-1}) 3296, 2914, 1715, 1619, 1590, 1518. HRMS (EI) *m/z*: [M^+] calcd for $C_{17}H_{15}NO_2$, 265.1103; found, 265.1099.

*7-((4-Methoxyphenyl)amino)-4-methyl-2H-chromen-2-one (**5da**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 10%−50% EtOAc/Hex provided the title compound as an orange solid (63.6 mg, 73%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.63 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 6.83 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.00 (d, *J* = 1.1 Hz, 1H), 3.75 (s, 3H), 2.33 (d, *J* = 1.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 160.5, 155.4, 155.2, 153.5, 149.5, 133.6, 126.4, 122.9, 114.7, 111.2, 110.5, 108.7, 98.4, 55.2, 18.0. FTIR (ATR, cm^{-1}) 3300, 2918, 1704, 1619, 1596, 1564, 1505. HRMS (EI) *m/z*: [M^+] calcd for $C_{17}H_{15}NO_3$, 281.1052; found, 281.1054.[36]

*7-((2,6-Dimethylphenyl)amino)-4-methyl-2H-chromen-2-one (**5ea**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 50:50:0 to 50:40:10 CH_2Cl_2/Hex/EtOAc provided the title compound as a tan solid (48.0 mg, 57%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.23 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.21−7.09 (m, 3H), 6.49 (bd, *J* = 8.1 Hz, 1H), 6.07 (br s, 1H), 5.95 (d, *J* = 1.1 Hz, 1H), 2.31 (d, *J* = 1.1 Hz, 3H), 2.14 (s, 6H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 160.5, 155.5, 153.6, 151.0, 136.8, 136.0, 128.5, 126.5, 126.5, 109.9, 109.8, 108.2, 97.1, 18.0, 17.8. FTIR (ATR, cm^{-1}) 3301, 2916, 1692, 1619, 1589, 1504. HRMS (EI) *m/z*: [M^+] calcd for $C_{18}H_{17}NO_2$, 279.1259; found, 279.1254.

*7-((3,5-Dimethoxyphenyl)amino)-4-methyl-2H-chromen-2-one (**5fa**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 25%−50% EtOAc/Hex provided the title compound as a yellow solid (43.6 mg, 45%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.86 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.03 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 2H), 6.17 (t, *J* = 2.2 Hz, 1H), 6.08 (d, *J* = 1.1 Hz, 1H), 3.73 (s, 6H), 2.36 (d, *J* = 1.0 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 161.2, 160.4, 154.9, 153.4, 147.5, 142.9, 126.4, 112.7, 111.7, 109.6, 100.9, 97.3, 94.2, 55.1, 18.0. FTIR (ATR, cm^{-1}) 3334, 1690, 1626, 1612, 1588, 1391. HRMS (EI) *m/z*: [M^+] calcd for $C_{18}H_{17}NO_4$, 311.1158; found, 311.1157.

*7-((3-Chloro-2-methylphenyl)amino)-4-methyl-2H-chromen-2-one (**5ga**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 20% EtOAc/Hex to 20% EtOAc/CH_2Cl_2 provided the title compound as a tan solid (89.6 mg, 96%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.50 (s, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.30−7.22 (m, 3H), 6.78 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 2.34 (d, *J* = 1.1 Hz, 3H), 2.24 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 160.9, 155.5, 154.0, 149.9, 141.2, 135.1, 130.8, 128.1, 126.9, 125.7, 123.1, 112.1, 111.6, 109.8, 100.2, 18.5, 15.5. FTIR (ATR, cm^{-1}) 3347, 1713, 1628, 1586, 1449, 1392. HRMS (EI) *m/z*: [M^+] calcd for $C_{17}H_{14}{}^{35}ClNO_2$, 299.0713; found, 299.0714.

*7-((2,4-Dibromophenyl)amino)-4-methyl-2H-chromen-2-one (**5ha**).* Synthesized according to General Procedure 2 on a 0.310 mmol scale using DMSO (4.6 mL) as the solvent. TLC analysis after heating the mixture for 24 h at 70 °C indicated significant remaining starting material. The reaction was heated for additional 24 h at 100 °C. After cooling to rt, the reaction was poured into 150 mL of 0.5 M HCl, and the resulting tan solid was filtered and washed with water. Chromatographic purification using a gradient eluent of 50:50:0−99:0:1 CH_2Cl_2/Hex/MeOH provided the title compound as a white solid (48.3 mg, 38%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.49 (s, 1H), 7.93 (s, *J* = 2.3 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.56 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.91 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.10 (d, *J* = 1.1 Hz, 1H), 2.36 (d, *J* = 1.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 160.3, 154.8, 153.4, 147.8, 139.0, 135.3, 131.6, 126.4, 125.4, 118.6, 115.9, 112.4, 112.0, 109.9, 101.2, 18.0. FTIR (ATR, cm^{-1}) 3323, 2920, 1699, 1609, 1579, 1494, 1388. HRMS (EI) *m/z*: [M^+] calcd for $C_{16}H_{11}{}^{79}Br_2NO_2$, 406.9157; found, 406.9156.

*Ethyl 3-((4-Methyl-2-oxo-2H-chromen-7-yl)amino)-benzoate (**5ia**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 25:25:50 CH_2Cl_2/EtOAc/Hex to 40:40:20 CH_2Cl_2/EtOAc/Hex provided the title compound as a yellow solid (52.6 mg, 52%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.10 (s, 1H), 7.76−7.73 (m, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.60−7.54 (m, 1H), 7.53−7.44 (m, 2H), 7.03 (dd, *J* = 8.7, 2.3, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.11 (d, *J* = 1.2 Hz, 1H), 4.32 (q, *J* = 7.1 Hz,

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2H), 2.37 (d, J = 1.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 165.6, 160.3, 154.9, 153.4, 147.1, 141.7, 131.1, 129.9, 126.6, 123.1, 122.3, 119.2, 112.6, 112.1, 109.9, 100.8, 60.8, 18.0, 14.2. FTIR (ATR, cm^{-1}) 3321, 1719, 1698, 1631, 1604, 1292. HRMS (EI) m/z: [M$^+$] calcd for $C_{19}H_{17}NO_4$, 323.1158; found, 323.1153.

*4-Methyl-7-(naphthalen-1-ylamino)-2H-chromen-2-one (**5ka**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 0%−1% MeOH/CH_2Cl_2 provided the title compound as an orange solid (62.3 mg, 67%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.96 (s, 1H), 8.08−8.01 (m, 1H), 8.00−7.93 (m, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.60−7.45 (m, 5H), 6.92 (dd, J = 8.7, 2.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.03 (d, J = 1.0 Hz, 1H), 2.34 (s, 3H). Spectral data are in agreement with literature values.[10]

*7-(Benzylamino)-4-methyl-2H-chromen-2-one (**5la**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 15%−30% EtOAc/Hex provided the title compound as a white solid (52.9 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.41−7.28 (m, 6H), 6.56 (dd, J = 8.7, 2.4 Hz, 1H), 6.49 (d, J = 2.3 Hz, 1H), 5.99 (d, J = 1.1 Hz, 1H), 4.64 (b, 1H), 4.40 (d, J = 5.6 Hz, 2H), 2.34 (d, J = 1.1 Hz, 3H). Spectral data are in agreement with literature values.[37]

*7-(Butylamino)-4-methyl-2H-chromen-2-one (**5ma**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 10%−30% EtOAc/Hex provided the title compound as a white solid (36.8 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.35 (d, J = 8.6 Hz, 1H), 6.50 (dd, J = 8.6, 2.4 Hz, 1H), 6.44 (d, J = 2.3 Hz, 1H), 5.98 (d, J = 1.1 Hz, 1H), 4.19 (br s, 1H), 3.18 (q, J = 6.3 Hz, 2H), 2.35 (d, J = 1.1 Hz, 3H), 1.70−1.58 (m, 2H), 1.52−1.38 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). Spectral data are in agreement with literature values.[38]

*7-Amino 4-Methyl-2H-chromen-2-one (**5na**).* Synthesized according to General Procedure 2. After 24 h of heating at 70 °C, the solvent was removed in vacuo, the residue was dissolved in EtOH (3 mL), and 6 M HCl (1 mL) was added. The resulting solution was heated to 90 °C in an oil bath for 5 h. After cooling, EtOH was removed in vacuo, the reaction was neutralized with sat aq $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over magnesium sulfate and concentrated in vacuo. Chromatographic purification using a gradient eluent of 0%−2% MeOH/CH_2Cl_2 provided the title compound as a pale-yellow solid (19.5 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.40 (d, J = 8.7 Hz, 1H), 6.56 (dd, J = 8.6, 2.2 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 6.09 (br s, 2H), 5.90 (d, J = 1.1 Hz, 1H), 2.30 (d, J = 1.1 Hz, 3H). Spectral data are in agreement with literature values.[39]

*7-(m-Tolylamino)-2H-chromen-2-one (**5cb**).* Synthesized according to General Procedure 2 on a 0.226 mmol scale. Chromatographic purification using a gradient eluent of 10:10:80 to 20:20:60 EtOAc/CH_2Cl_2:Hex provided the title compound as a yellow solid (46.5 mg, 82%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.84 (s, 1H), 7.88 (d, J = 9.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.04−6.98 (m, 2H), 6.94 (dd, J = 8.5, 2.2 Hz, 1H), 6.87−6.82 (m, 2H), 6.12 (d, J = 9.4 Hz, 1H), 2.30 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 160.6, 155.7, 148.2, 144.4, 140.8, 138.7, 129.4, 129.2, 123.2, 120.2, 116.9, 112.4, 110.6, 110.2, 99.7, 21.1. FTIR (ATR, cm^{-1}) 3306, 1693, 1586, 1512, 1329. HRMS (EI) m/z: [M$^+$] calcd for $C_{16}H_{13}NO_2$, 251.0946; found, 251.0946.

*3-Benzyl-4-methyl-7-(m-tolylamino)-2H-chromen-2-one (**5cc**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 10−30% EtOAc/Hex provided the title compound as a tan solid (82.2 mg, 75%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.76 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.30−7.13 (m, 6H), 7.03−6.96 (m, 3H), 6.87 (d, J = 2.3 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 3.92 (s, 2H), 2.38 (s, 3H), 2.29 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 161.5, 153.6, 148.5, 147.2, 141.2, 139.6, 138.7, 129.2, 128.4, 128.0, 126.5, 126.0, 122.8, 119.8, 119.2, 116.4, 112.5, 111.8, 99.9, 32.1, 21.2, 15.0. FTIR (ATR, cm^{-1}) 3323, 1699, 1628, 1596, 1528, 1359. HRMS (EI) m/z: [M$^+$] calcd for $C_{24}H_{21}NO_2$, 355.1572; found, 355.1569.

*6-Chloro-4-methyl-7-(m-tolylamino)-2H-chromen-2-one (**5cd**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 10−30% EtOAc/Hex provided the title compound as a yellow solid (65.3 mg, 70%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.16 (s, 1H), 7.78 (s, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.13−7.06 (m, 2H), 6.96 (d, J = 7.7 Hz, 1H), 6.85 (s, 1H), 6.13 (d, J = 1.1 Hz, 1H), 2.37 (d, J = 1.1 Hz, 3H), 2.31 (s, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6, ppm): δ 159.9, 153.2, 152.7, 144.5, 140.2, 138.8, 129.2, 126.1, 124.6, 122.7, 119.3, 116.6, 112.1, 110.5, 100.6, 21.0, 18.0. FTIR (ATR, cm^{-1}) 3314, 2919, 1722, 1599, 1545, 1531, 1389. HRMS (EI) m/z: [M$^+$] calcd for $C_{17}H_{14}{}^{35}ClNO_2$, 299.0713; found, 299.0716.

*7-(m-Tolylamino)-4-(trifluoromethyl)-2H-chromen-2-one (**5cf**).* Synthesized according to General Procedure 2 with heating at 100 °C for 30 h. Chromatographic purification using a gradient eluent of 10−25% EtOAc/Hex provided the title compound as a yellow solid (9.6 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.54 (dq, J = 8.9, 1.9 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.05−6.96 (m, 3H), 6.95 (d, J = 2.3 Hz, 1H), 6.87 (dd, J = 8.9, 2.3 Hz, 1H), 6.51 (s, 1H), 6.18 (br s, 1H), 2.38 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$, ppm): δ 160.1, 156.8, 149.2, 141.8 (q, J = 32.5 Hz), 139.9, 139.5, 129.7, 126.6, 125.6, 122.5, 121.9 (q, J = 275.4 Hz), 118.9, 113.1, 110.3 (q, J = 5.8 Hz), 105.8, 101.3, 21.6. FTIR (ATR, cm^{-1}) 3327, 1709, 1628, 1607, 1589, 1281. HRMS (EI) m/z: [M$^+$] calcd for $C_{17}H_{12}F_3NO_2$, 319.0820; found, 319.0813.

*7-(Benzylamino)-4-(trifluoromethyl)-2H-chromen-2-one (**5lf**).* Synthesized according to General Procedure 2. Chromatographic purification using a gradient eluent of 10−35% EtOAc/Hex provided the title compound as a bright yellow solid (15.5 mg, 16%). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 7.65 (t, J = 6.0 Hz, 1H), 7.42−7.31 (m, 5H), 7.30−7.21 (m, 1H), 6.76 (dd, J = 9.0, 2.3 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.45 (s, 1H), 4.41 (d, J = 6.0 Hz, 2H). Spectral data are in agreement with literature values.[40]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04653.

Full experimental details of reaction optimization, one-pot reactions, and mechanistic studies as well as ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

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REFERENCES

(1) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Simple Coumarins and Analogues in Medicinal Chemistry: Occurrence, Synthesis and Biological Activity. *Curr. Med. Chem.* **2005**, *12*, 887−916.

(2) Calcio Gaudino, E. C.; Tagliapietra, S.; Martina, K.; Palmisano, G.; Cravotto, G. Recent Advances and Perspectives in the Synthesis of Bioactive Coumarins. *RSC Adv.* **2016**, *6*, 46394−46405.

(3) Medina, F. G.; Marrero, J. G.; Macías-Alonso, M.; González, M. C.; Córdova-Guerrero, I.; Teissier García, A. G.; Osegueda-Robles, S. Coumarin Heterocyclic Derivatives: Chemical Synthesis and Biological Activity. *Nat. Prod. Rep.* **2015**, *32*, 1472−1507.

(4) Peng, X.-M.; L.V. Damu, G. L. V.; He Zhou, C.-H. Current Developments of Coumarin Compounds in Medicinal Chemistry. *Curr. Pharm. Des.* **2013**, *19*, 3884−3930.

(5) Cao, D.; Liu, Z.; Verwilst, P.; Koo, S.; Jangjili, P.; Kim, J. S.; Lin, W. Coumarin-Based Small-Molecule Fluorescent Chemosensors. *Chem. Rev.* **2019**, *119*, 10403−10519.

(6) Lavis, L. D.; Raines, R. T. Bright Building Blocks for Chemical Biology. *ACS Chem. Biol.* **2014**, *9*, 855−866.

(7) Grimm, J. B.; Lavis, L. D. Caveat fluorophore: an insiders' guide to small-molecule fluorescent labels. *Nat. Methods* **2022**, *19*, 149−158.

(8) Li, X.; Gao, X.; Shi, W.; Ma, H. Design Strategies for Water-Soluble Small Molecular Chromogenic and Fluorogenic Probes. *Chem. Rev.* **2014**, *114*, 590−659.

(9) Zambare, S.; Abhey, A.; Zambare, P.; N. Sangshetti, J.; Shinde, D. Recent Advances in the Synthesis of Coumarin Derivatives via Pechmann Condensation. *Curr. Org. Chem.* **2016**, *20*, 798−828.

(10) Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. The Quest for the Ideal Base: Rational Design of a Nickel Precatalyst Enables Mild, Homogeneous C-N Cross-Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 4500−4507.

(11) Joy, M. N.; Bodke, Y. D.; Khader, K. K. A.; Ali Padusha, M. S.; Sajith, A. M.; Muralidharan, A. A Rapid and Modified Approach for C-7 Amination and Amidation of 4-Methyl-7-Nonafluorobutylsulfonyloxy Coumarins under Microwave Irradiation. *RSC Adv.* **2014**, *4*, 19766−19777.

(12) Greaney, D. M.; Whalley, M. F. Recent Advances in the Smiles Rearrangement: New Opportunities for Arylation. *Synthesis* **2022**, *54*, 1908−1918.

(13) Holden, C. M.; Greaney, M. F. Modern Aspects of the Smiles Rearrangement. *Chem.—Eur. J.* **2017**, *23*, 8992−9008.

(14) Bunnett, J. F.; Zahler, R. E. Aromatic Nucleophilic Substitution Reactions. *Chem. Rev.* **1951**, *49*, 273−412.

(15) Bayles, R.; Johnson, M. C.; Maisey, R. F.; Turner, R. W. The Smiles Rearrangement of 2-Aryloxy-2-methylpropanamides. Synthesis ofN-Aryl-2-hydroxy-2-methylpropanamides. *Synthesis* **1977**, *1977*, 31−33.

(16) Bayles, R.; Johnson, M. C.; Maisey, R. F.; Turner, R. W. A Smiles Rearrangement Involving Non-Activated Aromatic Systems; the Facile Conversion of Phenols to Anilines. *Synthesis* **1977**, *1977*, 33−34.

(17) Coutts, I. G. C.; Southcott, M. R. The Conversion of Phenols to Primary and Secondary Aromatic Amines via a Smiles Rearrangement. *J. Chem. Soc., Perkin Trans. 1* **1990**, 767−771.

(18) Mizuno, M.; Yamano, M. A New Practical One-Pot Conversion of Phenols to Anilines. *Org. Lett.* **2005**, *7*, 3629−3631.

(19) Guilarte, V.; Castroviejo, M. P.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. Approaches to the Synthesis of 2,3-Dihaloanilines. Useful Precursors of 4-Functionalized-1H-indoles. *J. Org. Chem.* **2011**, *76*, 3416−3437.

(20) Xie, Y.-S.; Vijaykumar, B. V. D.; Jang, K.; Shin, H.-H.; Zuo, H.; Shin, D.-S. One-Pot Conversion of Phenols to Anilines via Smiles Rearrangement. *Tetrahedron Lett.* **2013**, *54*, 5151−5154.

(21) Yu, J.; Wang, Y.; Zhang, P.; Wu, J. Direct Amination of Phenols under Metal-Free Conditions. *Synlett* **2013**, *24*, 1448−1454.

(22) Teichert, J. F.; Feringa, B. L. Catalytic asymmetric conjugate addition of Grignard reagents to coumarins-synthesis of versatile chiral building blocks. *Chem. Commun.* **2011**, *47*, 2679−2681.

(23) Pisani, L.; Barletta, M.; Soto-Otero, R.; Nicolotti, O.; Mendez-Alvarez, E.; Catto, M.; Introcaso, A.; Stefanachi, A.; Cellamare, S.; Altomare, C.; Carotti, A. Discovery, Biological Evaluation, and Structure-Activity and −Selectivity Relationships of 6′-Substituted (E)-2-(Benzofuran-3(2H)-ylidene)-N-methylacetamides, a Novel Class of Potent and Selective Monoamine Oxidase Inhibitors. *J. Med. Chem.* **2013**, *56*, 2651−2664.

(24) Kumar, K. S.; Ramulu, M. S.; Kumar, N. P. Unexpected C-N bond formation via Smiles rearrangement: one pot synthesis of N-arylated coumarin/pyran derivatives. *New J. Chem.* **2018**, *42*, 11276−11279.

(25) Yang, Q.; Sheng, M.; Henkelis, J. J.; Tu, S.; Wiensch, E.; Zhang, H.; Zhang, Y.; Tucker, C.; Ejeh, D. E. Explosion Hazards of Sodium Hydride in Dimethyl Sulfoxide, N,N-Dimethylformamide, and N,N-Dimethylacetamide. *Org. Process Res. Dev.* **2019**, *23*, 2210−2217.

(26) Yang, Q.; Sheng, M.; Huang, Y. Potential Safety Hazards Associated with Using N,N-Dimethylformamide in Chemical Reactions. *Org. Process Res. Dev.* **2020**, *24*, 1586−1601.

(27) Use of 20 mol % Cs_2CO_3 afforded 30% yield and 45% as determined by ^{19}F NMR.

(28) Compound **5na′** was isolated as the primary component of a crude mixture of product, starting material, and minor amounts of unidentified byproducts and was assigned based on the following signals: ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.13 (b, 1H), 7.89-7.86 (m, 1H), 7.75-7.67 (m, 2H), 6.27 (d, J = 1.2 Hz, 1H), 5.74 (b,

1H), 4.04 (d, J = 3.8 Hz, 2H), 2.40 (d, J = 1.2 Hz, 3H). See Supporting Information for additional details.

(29) Bernasconi, C. F.; Gehriger, C. L.; De Rossi, R. H. Intermediates in Nucleophilic Aromatic Substitution. 16. Toward a Complete Characterization of the Mechanism of Nucleophilic Aromatic Substitution by an Amine. Kinetics of Spiro Meisenheimer Complexes Derived from N-Methylethanolamine. *J. Am. Chem. Soc.* **1976**, *98*, 8451−8459.

(30) Ratnakar, S. J.; Woods, M.; Lubag, A. J. M.; Kovács, Z.; Sherry, A. D. Modulation of Water Exchange in Europium(III) DOTA−Tetraamide Complexes via Electronic Substituent Effects. *J. Am. Chem. Soc.* **2008**, *130*, 6−7.

(31) Ganeshapillai, D.; Woo, L. W. L.; Thomas, M. P.; Purohit, A.; Potter, B. V. L. C-3- and C-4-Substituted Bicyclic Coumarin Sulfamates as Potent Steroid Sulfatase Inhibitors. *ACS Omega* **2018**, *3*, 10748−10772.

(32) Goud, E. Y.; Rao, B. K.; Thirupahi, G.; Hemasri, Y.; Rao, Ch. P.; Kumar, P. V.; Rao, Y. J. Synthesis of HighlyZ-Selective Coumarin Annulated Dioxocine, Dioxacindione and Macrocycles Using Grubbs' Second-Generation Catalyst. *ChemistrySelect* **2017**, *2*, 1170−1174.

(33) Kinoshita, M.; Negishi, M.; Sakai, H.; Hirano, T.; Mori, S.; Fujii, S.; Kagechika, H.; Tanatani, A. Development of 6-arylcoumarins as nonsteroidal progesterone antagonists. Structure-activity relationships and fluorescence properties. *Bioorg. Med. Chem.* **2016**, *24*, 5602−5610.

(34) García-Beltrán, O.; Yañez, O.; Caballero, J.; Galdámez, A.; Mena, N.; Nuñez, M. T.; Cassels, B. K. Synthesis of Coumarin Derivatives as Fluorescent Probes for Membrane and Cell Dynamics Studies. *Eur. J. Med. Chem.* **2014**, *76*, 79−86.

(35) Irikura, M.; Tanaka, T.; Takadate, A.; Goya, S.; Otagiri, M. Interaction of Fluorescent Probe 7-Anilino-4-Methylcoumarin-3-(p)-Benzoic Acid with Egg Albumin. *Anal. Sci.* **1997**, *13*, 53−58.

(36) Characterization data for compounds **5ba** and **5da** are not consistent with those reported in ref 11. Full characterization is provided for **5da** and is consistent with all structural analogues. NMR data for **5ba** are consistent with previous reports as indicated.

(37) Symeonidis, T. S.; Hadjipavlou-Litina, D. J.; Litinas, K. E. Synthesis Through Three-Component Reactions Catalyzed by FeCl3of Fused Pyridocoumarins as Inhibitors of Lipid Peroxidation. *J. Heterocycl. Chem.* **2014**, *51*, 642−647.

(38) Liang, D.; Fan, Y.; Yang, Z.; Zhang, Z.; Liu, M.; Liu, L.; Jiang, C. Discovery of Coumarin-Based Selective Aldehyde Dehydrogenase 1A1 Inhibitors with Glucose Metabolism Improving Activity. *Eur. J. Med. Chem.* **2020**, *187*, 111923.

(39) Ast, S.; Rutledge, P. J.; Todd, M. H. Reversing the Triazole Topology in a Cyclam-Triazole-Dye Ligand Gives a 10-Fold Brighter Signal Response to Zn 2+ in Aqueous Solution. *Eur. J. Inorg. Chem.* **2012**, *2012*, 5611−5615.

(40) Bissell, E. R.; Larson, D. K.; Croudace, M. C. Some 7-Substituted-4-(Trifluoromethyl)Coumarins. *J. Chem. Eng. Data* **1981**, *26*, 348−350.

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