JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

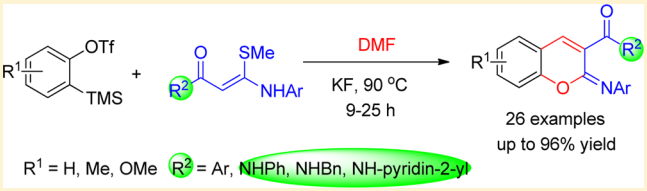
Direct Construction of 2-Aryliminochromenes from Arynes, *N,S*-Keteneacetals, and DMF

Li-Rong Wen, Ning-Ning Man, Wen-Kui Yuan, and Ming Li*

State Key Laboratory Base of Eco-Chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P. R. China

Supporting Information

ABSTRACT: A concise and direct synthetic strategy for the construction of 2-aryliminochromene skeleton by cascade three-component coupling reaction of arynes, *N,S*-keteneacetals, and DMF in good yields has been disclosed. The process demonstrates the first example of aryne chemistry combined with *N,S*-keteneacetals. Using this strategy, an expeditious synthesis of biologically important arylimino-2*H*-chromene-3-carboxamides was achieved.



INTRODUCTION

2-Aryliminochromenes, one of the most important classes of benzopyran compounds, constitute a core skeleton of biologically active compounds. For example, *N*-(2*H*-chromen-2-ylidene)arylamines have been investigated as inhibitors of aldo-keto reductase (AKR) 1B10, which are regarded as promising therapeutics for the treatment of cancer[1] and inhibitors of β-secretase (BACE1), which are potentially important molecules for the treatment of Alzheimer's disease (AD)[2] (Figure 1). Furthermore, they also constitute a class of small molecule fluorophores, which are cell membrane permeable with low cytotoxicity and able to selectively stain organelles in living cells[3] (Figure 1).

A number of protocols for the synthesis of 2-aryliminochromenes have been reported by various organic or pharmaceutical chemists.[1a,2−4] Utility of salicylaldehyde as a synthon is a classical method to construct 2-aryliminochromenes, but it requires two reaction steps[3] (Scheme 1, top). However, an approach to directly construct the 2-aryliminochromene skeleton in one pot has not been explored. It is of great importance to explore a novel and efficient synthetic method to meet increasing organic or pharmaceutical research demand.

A rapidly increasing recognition of the rich and fascinating chemistry of *N,S*-keteneacetals in organic synthesis has emerged, especially in recent years.[5] Reactions of *N,S*-keteneacetals with a variety of biselectrophilic groups have so far been applied to make five- and six-membered and fused heterocycles.[6] The utility of arynes, known as highly reactive intermediates, has been well recognized.[7] Aryne-based multicomponent reactions (MCRs) are one of the most popular multicomponent condensations due to their diversity of bond-forming processes and high levels of chemo- and regioselectivities.[8] However, the synthetic utility of *N,S*-keteneacetals as nucleophiles in aryne-based MCRs has not been explored up to now.

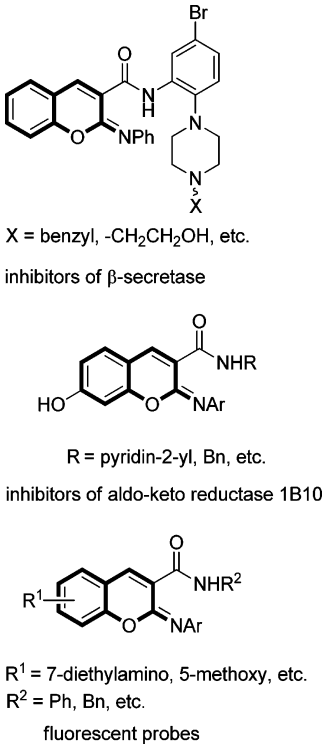


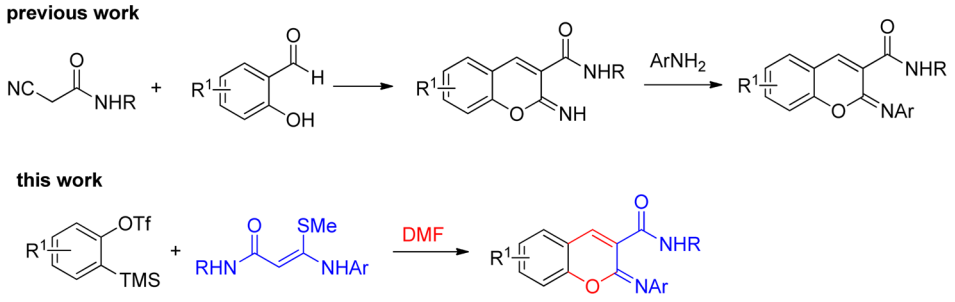
Figure 1. Selected pharmaceuticals and fluorescent probes containing 2-aryliminochromene.

Inspired by the pioneering results from the Miyabe group, in which highly reactive intermediates, *o*-quinone methides (*o*-QMs), might be formed by [2 + 2] π-bond cyclization of an aryne with DMF,[9] and in continuation of our ongoing research

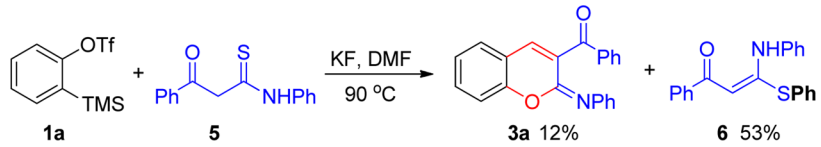
Received: April 15, 2016
Published: June 6, 2016

DOI: 10.1021/acs.joc.6b00843
J. Org. Chem. 2016, 81, 5942−5948

Scheme 1



Scheme 2. Reaction of 1a with β-Ketothioamide 5



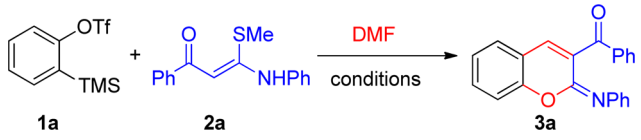
interest in the synthesis of heterocycles by utilizing β-ketothioamides as synthons,[10] we turned our attention to simultaneously utilize these two fascinating synthons to develop a new and direct strategy for the synthesis of 2-aryliminochromene derivatives via a three-component reaction (Scheme 1, bottom).

RESULTS AND DISCUSSION

Initially, the reaction of the Kobayashi precursor (2-trimethylsilylphenyl triflate) (**1a**) with β-ketothioamide **5** (mole ratio 2:1) in the presence of KF in DMF was investigated (Scheme 2), but only 12% yield of target product 3-benzoyl-2-phenyliminochromene **3a** was obtained together with 53% yield of S-phenylated β-ketothioamide **6**, which was confirmed by ^{1}H NMR (Figure S1 in Supporting Information (SI)). This result stimulated our interest in exploring the reaction of **1a** with S-methylated β-ketothioamide (**2a**). Gratifyingly, product **3a** was obtained in 59% yield (Table 1, entry 1). Then we commenced screening the optimal reaction conditions to get **3a** efficiently using a 2:1 mole ratio of **1a** and **2a**. The results are summarized in Table 1.

Initially, the ratio of **1a** and **2a** was investigated, and the result showed that increasing or decreasing the amount of **1a** did not improve the yield of **3a** (Table 1, entries 1−3). Next, various fluoride sources were screened in 4 mL of DMF at 80 °C, and the results revealed that KF was the best choice for the reaction, whereas other fluoride sources such as KF/18-crown-6, CsF, TBAT, and TBAF did not give satisfactory results (Table 1, entries 4−7). The effect of temperature on the reaction was evaluated, and the results suggested that 90 °C favored this reaction (entries 8−10). Additionally, the effect of solvent on the reaction was also tested in THF or CH_3CN with 10 equiv of DMF at 90 °C, but only trace **3a** was observed by TLC (entries 11 and 12). Next, the amount of DMF was investigated, and yield of **3a** was increased to 71% in 1 mL DMF (c = 0.2 M) (entries 13−15). Finally, to promote benzyne to react with S-methylated β-ketothioamide (**2a**), dropwise addition of **1a** was tried over 7 or 9 h (entries 16 and 17). To our delight, the yield of **3a** was improved up to 80% within 9 h. Unfortunately, when 4 Å molecular sieves was added to remove trace water in the reaction system, the yield of **3a** was not increased (entry 18). Consequently, the optimal reaction conditions were established by employing **1a** and **2a** in a ratio of 2:1 in the presence of KF (8.0 equiv) in DMF (c = 0.2 M) at 90 °C for 25 h.

Table 1. Screening of Optimal Reaction Conditions for 3a[a]



entry	1a:2a	F$^-$ source	DMF (mL)	temp (°C)	time (h)	yield (%)[b]
1	2:1	KF	4	80	24	59
2	1.5:1	KF	4	80	24	51
3	2.5:1	KF	4	80	24	54
4	2:1	KF/18-crown-6	4	80	24	57
5	2:1	CsF	4	80	24	complex
6	2:1	TBAT[c]	4	80	24	47
7	2:1	TBAF[d]	4	80	24	50
8	2:1	KF	4	60	24	trace
9	2:1	KF	4	90	24	62
10	2:1	KF	4	100	24	56
11	2:1	KF	0.3	90	24	trace[e]
12	2:1	KF	0.3	90	24	trace[f]
13	2:1	KF	2	90	24	63
14	2:1	KF	1	90	24	71
15	2:1	KF	0.5	90	24	61
16	2:1	KF	1	90	25	80[g]
17	2:1	KF	1	90	23	73[h]
18	2:1	KF	1	90	25	75[i]

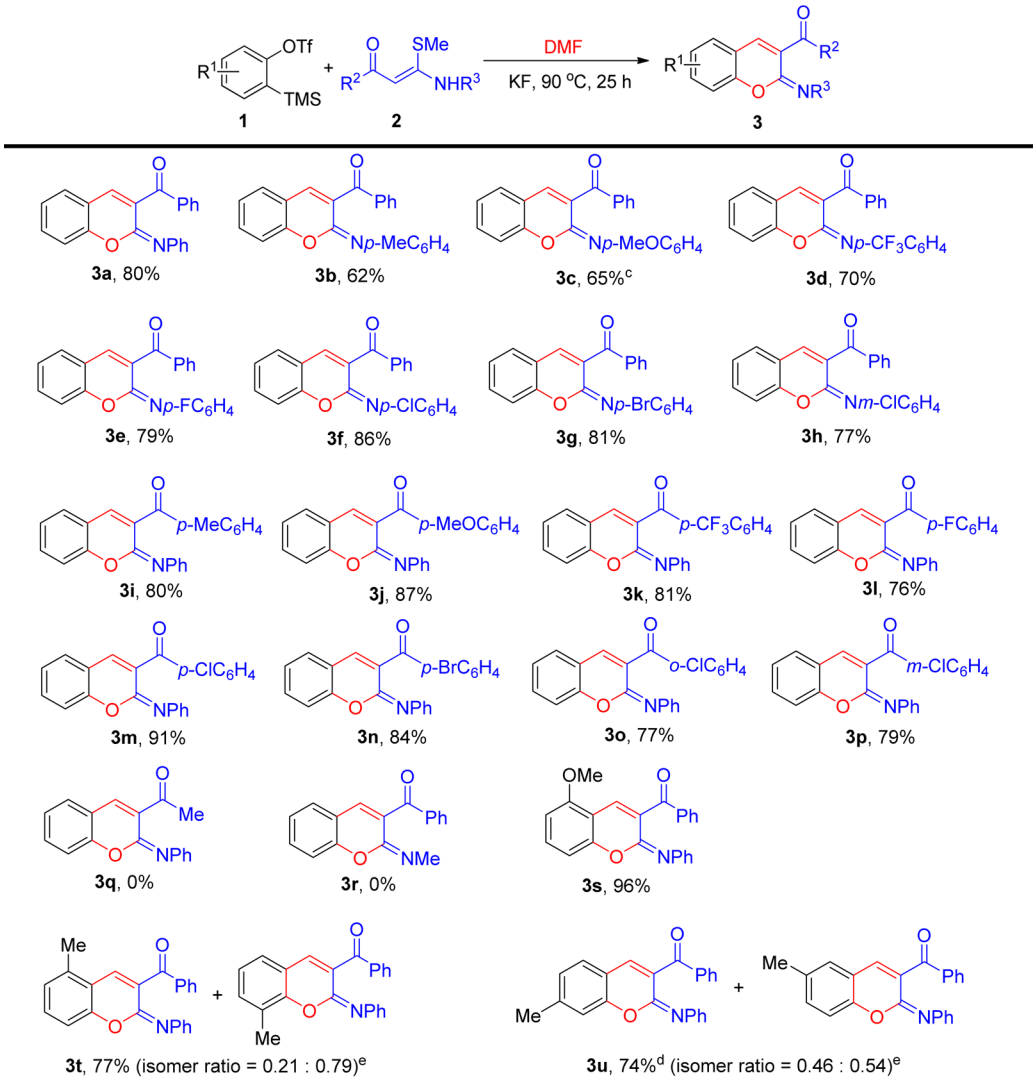
[a]Reaction conditions unless otherwise noted: **1a** (2 equiv), **2a** (0.2 mmol), and F$^-$ source (8 equiv) in sealed tube. [b]Isolated yield. [c]TBAT = $(Bu_4N)Ph_3SiF_2$. [d]TBAF = $(Bu_4N)F$. [e]CH_3CN as solvent. [f]THF as solvent. [g]**1a** was added in 9 h. [h]**1a** was added in 7 h. [i]400 mg 4 Å molecular sieves was added.

With the optimal conditions in hand, we next turned our attention to explore substrate scope by testing various aryne precursors **1** and *N*,*S*-keteneacetals **2**, and the results are summarized in Tables 2 and 3.

As can be seen from Table 2, for substrates **2**, when R^2 and R^3 are various aryl groups bearing both electron-donating and electron-withdrawing groups, *N*,*S*-keteneacetals were transformed smoothly into the desired products in good yields

DOI: 10.1021/acs.joc.6b00843
J. Org. Chem. 2016, 81, 5942−5948

Table 2. Substrate Scope for the Synthesis of 3[a,b]



[a]Reaction conditions: **1** (2 equiv), **2** (0.2 mmol), KF (8 equiv) in DMF (c = 0.2 M), and **1** was added dropwise over 9 h. [b]Isolated yields. [c]t-BuOK (0.2 mmol) was added. [d]Purified by preparative TLC. [e]Isomer ratio was determined by ^{1}H NMR.

(**3a**–**p**). When R^3 is 4-$OCH_3C_6H_4$, the reaction did not occur under the standard conditions, but when 1 equiv of t-BuOK was added, 65% yield of **3c** was obtained. Additionally, when R^2 or R^3 is an alkyl group such as methyl, no product was obtained and starting materials **2** could be recovered (**3q**–**r**). Moreover, the effect of the arynes was subsequently explored. When the o-OCH_3-substituted aryne (**1b**) was used, only single regioselective isomer **3s** was afforded, but when o- or m-CH_3-substituted arynes (**1c** or **1d**) were employed, the products were obtained as a mixture of two regioisomers (**3t** and **3u**). This observation was in agreement with a previous report.[7h]

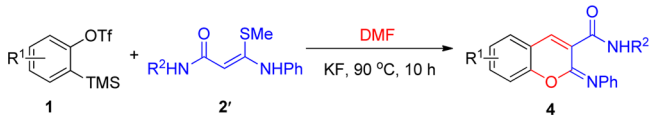
Given the importance of 2-arylimino-2*H*-chromene-3-carboxamides in biologically relevant molecules,[1−3] we next explored the reaction of (*Z*)-N-substituted-3-(methylthio)-3-(phenylamino)acrylamides **2′** with various arynes **1** under the above conditions (Table 3). Gratifyingly, the expected products phenylimino-2*H*-chromene-3-carboxamides **4** were obtained in good to excellent yields. Moreover, the reaction time was shorter than those reactions of **1** with **2**, just needing 9−10 h without dropwise addition of arynes **1**, suggesting that **2′** might have high nucleophilicity compared to **2**. Notably, when the o-OCH_3-substituted aryne (**1b**) was employed to react with **2′**, the high regioselectivity for products **4d** and **4e** was achieved, while o-CH_3-substituted aryne (**1c**) gave two regioisomeric products **4f** and **4g**.

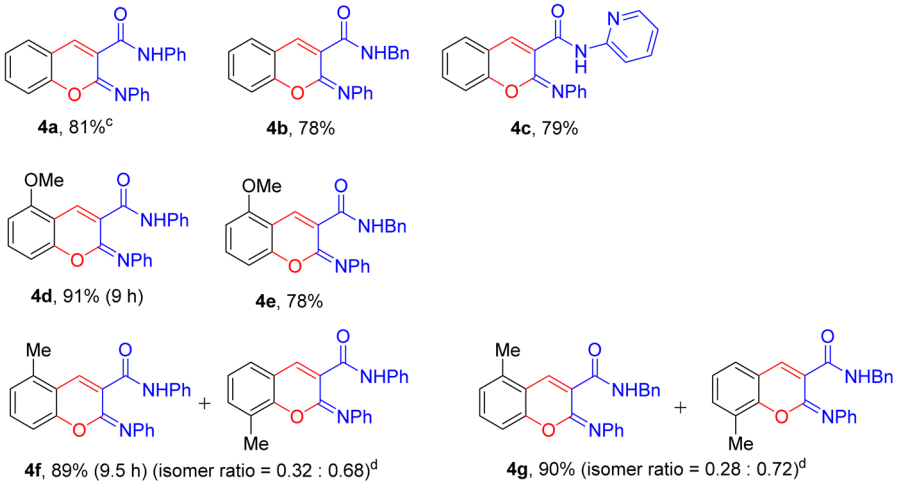
The structures of all new compounds **3** and **4** were identified by their ^{1}H NMR, ^{13}C NMR, and HRMS spectra and unequivocally confirmed by X-ray diffraction analysis of the monocrystal of **3a** (Figure S2 in SI).

Based on the above experimental results and relevant reports,[8g,9] a plausible reaction mechanism is depicted in Scheme 3. First, benzyne **1a′** is generated from Kobayashi precursor **1a** in the presence of KF. Then four-membered intermediate **A** is formed by [2 + 2] π-bond cyclization of **1a′** with DMF, which isomerizes to an o-quinone methide (o-QM) via ring-opening. Subsequently, the o-QM is trapped by *N*,*S*-keteneacetals **2′** to give formal [4 + 2] adduct **B**. Finally, the desired product **4** is afforded from intermediate **B** with elimination of dimethylamine and methyl mercaptan.

DOI: 10.1021/acs.joc.6b00843
J. Org. Chem. 2016, 81, 5942−5948

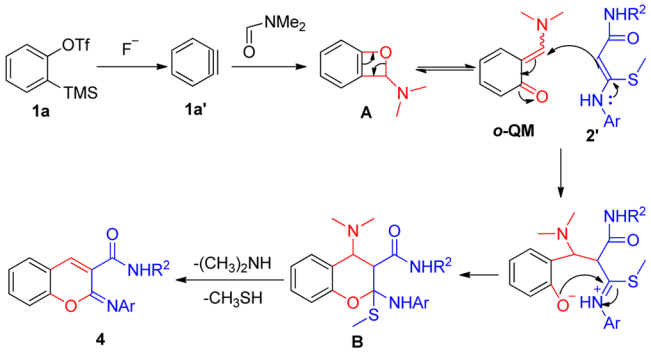
Table 3. Synthesis of Phenylimino-2*H*-chromene-3-carboxamides 4[a,b]





[a]Reaction conditions: **1** (2 equiv), **2′** (0.2 mmol), and KF (8 equiv) in DMF (c = 0.2 M). [b]Isolated yields. [c]Purified by washing with hot MeOH three times. [d]Isomer ratio was determined by ^{1}H NMR.

Scheme 3. Proposed Mechanism for the Formation of 4



CONCLUSION

In summary, we have developed a new transition-metal-free multicomponent coupling cyclization reaction for the strategy of directly constructing 3-acyl-2-aryliminochromene derivatives from arynes, *N*,*S*-keteneacetals, and DMF. This transformation proceeded smoothly via a route involving the trapping reaction of *o*-quinone methide intermediates and afforded arylimino-2*H*-chromene-3-carboxamides as pharmaceutical and fluorescent probes in moderate to good yields. Due to the high formation efficiency of the 3-benzoyl-2-aryliminochromene skeleton and the promising utilization of the arylimino-2*H*-chromene-3-carboxamide derivatives, this methodology may be of great interest to organic and pharmaceutical chemists.

EXPERIMENTAL SECTION

General Experimental Methods. All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise specified. *N*,*N*-Dimethylformamide (DMF) was further distilled from $MgSO_4$ and stored over 4 Å molecular sieves. All reagents were weighed and handled in air at room temperature. Melting points were recorded on a microscopic melting apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz in $CDCl_3$ or DMSO-d_6, respectively. Chemical shifts are reported in δ (ppm) relative to TMS. IR spectra were recorded on an FT-IR spectrometer, and only major peaks are reported in cm^{-1}. HRMS spectra were recorded on two different spectrometers with an ESI source. The X-ray single-crystal diffraction was performed on a CCD area detector. The substrates **2** were prepared according to a reported procedure,[11] and **2′** were prepared according to the literature.[12]

General Procedure for the Synthesis of Compounds 3 (3a for example). A clean sealed tube was baked in vacuum to remove water vapor before use. To a stirred solution of compound **2a** (51.1 mg, 0.2 mmol) in anhydrous DMF (1 mL) was added KF (92.7 mg, 1.6 mmol). The mixture was degassed with N_2 three times and heated to 90 °C. Then compound **1a** (93.2 uL, 119.3 mg, 0.4 mmol) was added dropwise over 9 h. The reaction mixture was stirred at 90 °C for another 16 h. After reaction completion as monitored by TLC, the reaction system was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phases were washed with aq NaCl (20 mL × 5), dried over $MgSO_4$, and concentrated in vacuum. The residue was recrystallized from EtOH to obtain pure product.

(Z)-Phenyl(2-(phenylimino)-2H-chromen-3-yl)methanone ***(3a).*** Isolated yield 52 mg (80%); yellow solid; mp 135−137 °C; R_f 0.48 (PE:EA = 15:1). IR (KBr) ν 3058, 3033, 1673, 1651, 1601, 1589, 1572, 1484, 1234, 1183, 764, 756, 708, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 7.40 Hz, 2H), 7.59 (t, J = 7.40 Hz, 1H), 7.47 (t, J = 7.40 Hz, 2H), 7.42−7.37 (m, 3H), 7.29−7.26 (m, 2H), 7.18 (t, J = 7.33 Hz, 1H), 7.11 (d, J = 8.25 Hz, 1H), 7.08−7.05 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.2, 153.6, 146.7, 145.2, 136.6, 135.1, 133.4, 132.3, 131.6, 129.6, 128.4, 128.3, 124.2, 124.1, 122.8, 119.0, 115.9; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{22}H_{16}NO_2$, 326.1181, found 326.1185.

(Z)-Phenyl(2-(p-tolylimino)-2H-chromen-3-yl)methanone ***(3b).*** Isolated yield 42 mg (62%); yellow solid; mp 129−131 °C; R_f 0.47 (PE:EA = 15:1). IR (KBr) ν 3066, 3023, 2918, 1672, 1636, 1589, 1572, 1505, 1455, 1238, 832, 761, 746, 705 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 7.45 Hz, 2H), 7.58 (t, J = 7.42 Hz, 1H), 7.46 (t, J = 7.75 Hz, 2H), 7.42−7.36 (m, 3H), 7.16 (t, J = 7.35 Hz, 1H), 7.12 (d, J = 8.25 Hz, 1H), 7.08 (d, J = 8.15 Hz, 2H), 7.00 (d, J = 8.20 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3,

DOI: 10.1021/acs.joc.6b00843
J. Org. Chem. 2016, 81, 5942−5948

153.7, 146.4, 142.4, 136.5, 134.7, 133.9, 133.4, 132.4, 131.6, 129.6, 129.0, 128.4, 128.3, 124.0, 123.0, 119.1, 115.9, 21.0; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{23}H_{18}NO_2$, 340.1338, found 340.1345.

*(Z)-(2-((4-Methoxyphenyl)imino)-2H-chromen-3-yl)(phenyl)-methanone (**3c**).* Isolated yield 46 mg (65%); yellow solid; mp 140−145 °C; R_f 0.45 (PE:EA = 15:1). IR (KBr) ν 3057, 2934, 2839, 1672, 1633, 1602, 1588, 1505, 1454, 1247, 1173, 1031, 830, 751, 704 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.99 (d, J = 7.75 Hz, 2H), 7.73 (s, 1H), 7.65 (t, J = 7.35 Hz, 1H), 7.60 (d, J = 7.45 Hz, 1H), 7.54−7.48 (m, 3H), 7.26 (t, J = 7.48 Hz, 1H), 7.21 (d, J = 8.20 Hz, 1H), 7.04 (d, J = 8.75 Hz, 2H), 6.84 (d, J = 8.80 Hz, 2H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.3, 156.8, 153.5, 146.6, 138.2, 136.7, 135.0, 134.2, 132.4, 132.1, 129.8, 129.2, 125.0, 124.8, 119.5, 116.0, 114.4, 55.7; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{23}H_{17}NO_3$, 356.1287, found 356.1275.

*(Z)-Phenyl(2-((4-(trifluoromethyl)phenyl)imino)-2H-chromen-3-yl)methanone (**3d**).* Isolated yield 55 mg (70%); yellow solid; mp 137−139 °C; R_f 0.46 (PE:EA = 15:1). IR (KBr) ν 3054, 1676, 1637, 1589, 1572, 1456, 1233, 1186, 1109, 847, 759, 747, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 7.50 Hz, 2H), 7.60 (t, J = 7.38 Hz, 1H), 7.52 (d, J = 8.30 Hz, 2H), 7.51−7.47 (m, 3H), 7.46−7.41 (m, 2H), 7.21 (t, J = 7.32 Hz, 1H), 7.11−7.09 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.8, 153.2, 149.6, 148.7, 137.1, 136.4, 134.2, 132.7, 131.0, 129.9, 129.4, 129.1, 126.3, 125.0, 124.9 (q, $^1J_{C-F}$ = 271.4 Hz), 124.5 (q, $^2J_{C-F}$ = 31.7 Hz), 123.1, 119.2, 116.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ −60.3; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{23}H_{15}NO_2F_3$, 394.1055, found 394.1062.

*(Z)-(2-((4-Fluorophenyl)imino)-2H-chromen-3-yl)(phenyl)-methanone (**3e**).* Isolated yield 54 mg (79%); yellow solid; mp 169−171 °C; R_f 0.45 (PE:EA = 15:1). IR (KBr) ν 3056, 1670, 1631, 1604, 1500, 1241, 1188, 840, 761, 742, 706 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.03 (d, J = 7.65 Hz, 2H), 7.83 (s, 1H), 7.68−7.64 (m, 2H), 7.56−7.51 (m, 3H), 7.29 (t, J = 7.40 Hz, 1H), 7.20 (d, J = 8.20 Hz, 1H), 7.13−7.05 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.8, 164.0 (d, $^1J_{C-F}$ = 240.5 Hz), 158.0, 152.5, 146.5, 141.2, 140.7, 138.9, 137.2, 136.3, 134.5, 134.0, 133.9, 129.6, 129.5, 129.4, 124.0, 120.6 (d, $^2J_{C-F}$ = 20.3 Hz), 120.4; ^{19}F NMR (376 MHz, DMSO-d_6) δ −118.9; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{22}H_{15}NO_2F$, 344.1087, found 344.1078.

*(Z)-(2-((4-Chlorophenyl)imino)-2H-chromen-3-yl)(phenyl)-methanone (**3f**).* Isolated yield 62 mg (86%); yellow solid; mp 163−165 °C; R_f 0.48 (PE:EA = 15:1). IR (KBr) ν 3066, 1672, 1630, 1599, 1577, 1569, 1483, 1241, 1190, 835, 761, 745, 713 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.03 (d, J = 6.30 Hz, 2H), 7.86 (s, 1H), 7.69−7.63 (m, 2H), 7.56−7.51 (m, 3H), 7.34−7.28 (m, 3H), 7.20 (d, J = 7.40 Hz, 1H), 7.04 (d, J = 7.10 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.9, 153.2, 148.1, 144.5, 136.4, 134.2, 132.5, 131.3, 129.8, 129.3, 129.1, 129.0, 128.4, 124.9, 124.6, 119.2, 116.0; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{22}H_{15}NO_2Cl$, 360.0791, found 360.0785.

*(Z)-(2-((4-Bromophenyl)imino)-2H-chromen-3-yl)(phenyl)-methanone (**3g**).* Isolated yield 65 mg (81%); yellow solid; mp 148−150 °C; R_f 0.49 (PE:EA = 15:1). IR (KBr) ν 3073, 1668, 1633, 1598, 1571, 1480, 1236, 1186, 833, 747, 713, 685 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.03 (d, J = 7.65 Hz, 2H), 7.86 (s, 1H), 7.69−7.65 (m, 2H), 7.56−7.51 (m, 3H), 7.45 (d, J = 8.40 Hz, 2H), 7.29 (t, J = 7.45 Hz, 1H), 7.20 (d, J = 8.25 Hz, 1H), 6.98 (d, J = 8.35 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.9, 153.2, 148.1, 144.9, 136.4, 134.2, 132.5, 132.0, 131.4, 129.8, 129.4, 129.2, 125.1, 125.0, 119.3, 116.5, 116.0; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{22}H_{15}NO_2Br$, 404.0286, found 404.0279.

*(Z)-(2-((3-Chlorophenyl)imino)-2H-chromen-3-yl)(phenyl)-methanone (**3h**).* Isolated yield 55 mg (77%); yellow solid; mp 124−126 °C; R_f 0.45 (PE:EA = 15:1). IR (KBr) ν 3082, 1659, 1651, 1605, 1587, 1571, 1454, 1238, 1087, 803, 753, 740, 708, 685 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.06 (s, 1H), 8.00 (d, J = 7.70 Hz, 1H), 7.89 (s, 1H), 7.74 (d, J = 7.70 Hz, 1H), 7.66 (d, J = 7.35 Hz, 1H), 7.57 (d, J = 7.88 Hz, 1H), 7.53 (d, J = 7.65 Hz, 1H), 7.31−7.28 (m, 3H), 7.16 (d, J = 8.25 Hz, 1H), 7.06 (t, J = 7.30 Hz, 1H), 7.00 (t, J = 7.75 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.1, 153.5, 147.4, 145.5, 138.5, 137.0, 134.0, 133.7, 132.6, 131.1, 130.8, 129.4, 129.1, 128.4, 124.8, 124.4, 122.7, 119.2, 115.9; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{22}H_{15}NO_2Cl$, 360.0791, found 360.0781.

*(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(p-tolyl)methanone (**3i**).* Isolated yield 54 mg (80%); yellow solid; mp 164−166 °C; R_f 0.47 (PE:EA = 15:1). IR (KBr) ν 3062, 2923, 1664, 1631, 1604, 1581, 1570, 1244, 1173, 833, 762, 751, 687 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.93 (d, J = 7.55 Hz, 2H), 7.78 (s, 1H), 7.63 (d, J = 7.25 Hz, 1H), 7.51 (t, J = 7.48 Hz, 1H), 7.35 (d, J = 7.55 Hz, 2H), 7.31−7.28 (m, 3H), 7.15 (d, J = 8.05 Hz, 1H), 7.06 (t, J = 7.10 Hz, 1H), 7.01 (d, J = 7.45 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.5, 153.3, 147.4, 145.6, 144.7, 135.6, 134.0, 132.3, 131.8, 130.0, 129.7, 129,2, 129.1, 124.8, 124.4, 122.7, 119.3, 115.9, 21.6; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{23}H_{18}NO_2$, 340.1338, found 340.1341.

*(Z)-(4-Methoxyphenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone(**3j**).* Isolated yield 62 mg (87%); yellow solid; mp 157−159 °C; R_f 0.49 (PE:EA = 15:1). IR (KBr) ν 3056, 2929, 2839, 1645, 1596, 1570, 1258, 1169, 840, 766, 753, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.65 Hz, 2H), 7.41−7.36 (m, 3H), 7.30−7.25 (m, 2H), 7.16 (t, J = 7.45 Hz, 1H), 7.10−7.05 (m, 4H), 6.95 (d, J = 8.65 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 191.4, 164.2, 153.2, 147.5, 145.7, 135.2, 132.6, 132.4, 132.3, 132.0, 129.3, 129.1, 124.8, 124.4, 122.8, 119.3, 115.9, 114.5, 56.1; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{23}H_{18}NO_3$, 356.1287, found 356.1295.

*(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(4-(trifluoromethyl)-phenyl)methanone (**3k**).* Isolated yield 64 mg (81%); yellow solid; mp 112−114 °C; R_f 0.45 (PE:EA = 15:1). IR (KBr) ν 3072, 1676, 1637, 1602, 1585, 1484, 1455, 1124, 1072, 862, 759, 753, 705 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.23 (d, J = 7.93 Hz, 2H), 7.95 (s, 1H), 7.90 (d, J = 7.93 Hz, 2H), 7.68 (d, J = 7.32 Hz, 1H), 7.54 (t, J = 7.63 Hz, 1H), 7.31−7.27 (m, 3H), 7.18 (d, J = 8.25 Hz, 1H), 7.06 (t, J = 7.33 Hz, 1H), 6.98 (d, J = 7.75 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.5, 153.5, 147.4, 145.4, 139.9, 137.4, 132.8, 130.8, 130.4, 129.6, 129.1, 126.1, 124.9, 124.5, 122.7, 119.2, 116.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.5; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{23}H_{15}NO_2F_3$, 394.1055, found 394.1049.

*(Z)-(4-Fluorophenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone (**3l**).* Isolated yield 52 mg (76%); yellow solid; mp 149−151 °C; R_f 0.48 (PE:EA = 15:1). IR (KBr) ν 3066, 1669, 1631, 1596, 1581, 1505, 1482, 1243, 1152, 861, 759, 690 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.13 (t, J = 6.63 Hz, 2H), 7.84 (s, 1H), 7.64 (d, J = 7.35 Hz, 1H), 7.52 (t, J = 7.55 Hz, 1H), 7.37 (t, J = 8.50 Hz, 2H), 7.31−7.27 (m, 3H), 7.16 (d, J = 8.15 Hz, 1H), 7.06 (t, J = 7.18 Hz, 1H), 7.01 (d, J = 7.65 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 191.9, 165.9 (d, $^1J_{C-F}$ = 259.0 Hz), 153.5, 147.5, 145.6, 136.3, 133.4, 133.0, 132.9, 132.6, 131.5, 129.4, 129.2, 124.9, 124.6, 122.9, 119.4, 116.3 (d, $^2J_{C-F}$ = 20.9 Hz), 116.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ −104.9; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{22}H_{15}NO_2F$, 344.1087, found 344.1092.

*(Z)-(4-Chlorophenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone (**3m**).* Isolated yield 65 mg (91%); yellow solid; mp 168−170 °C; R_f 0.49 (PE:EA = 15:1). IR (KBr) ν 3073, 1663, 1635, 1603, 1583, 1487, 1453, 1242, 1183, 809, 764, 744, 685 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.06 (d, J = 8.45 Hz, 2H), 7.86 (s, 1H), 7.65 (d, J = 7.15 Hz, 1H), 7.60 (d, J = 8.45 Hz, 2H), 7.52 (t, J = 7.65 Hz, 1H), 7.31−7.27 (m, 3H), 7.16 (d, J = 8.25 Hz, 1H), 7.06 (t, J = 7.32 Hz, 1H), 7.00 (d, J = 7.75 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.2, 153.5, 147.5, 145.5, 139.1, 136.6, 135.3, 132.7, 131.7, 131.2, 129.4, 129.3, 129.2, 124.9, 124.5, 122.8, 119.3, 116.0; HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{22}H_{15}NO_2Cl$, 360.0791, found 360.0785.

*(Z)-(4-Bromophenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone (**3n**).* Isolated yield 68 mg (84%); yellow solid; mp 176−178 °C; R_f 0.45 (PE:EA = 15:1). IR (KBr) ν 3055, 1643, 1602, 1586, 1486, 1453, 1242, 1188, 848, 753, 687 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.97 (d, J = 7.93 Hz, 2H), 7.86 (s, 1H), 7.75 (d, J = 7.93 Hz, 2H), 7.65 (d, J = 7.32 Hz, 1H), 7.52 (t, J = 7.93 Hz, 1H), 7.31−7.27 (m, 3H), 7.16 (d, J = 8.54 Hz, 1H), 7.06 (t, J = 7.02 Hz, 1H), 7.01 (d, J = 7.94 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.4, 153.5, 147.5, 145.6, 136.7, 135.7, 132.7, 132.3, 131.8, 131.2, 129.5,

DOI: 10.1021/acs.joc.6b00843
J. Org. Chem. 2016, 81, 5942−5948

129.2, 128.4, 124.9, 124.6, 122.8, 119.3, 116.1; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{22}H_{15}NO_2Br$, 404.0286, found 404.0289.

*(Z)-(2-Chlorophenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone (**3o**).* Isolated yield 55 mg (77%); yellow solid; mp 136−138 °C; R_f 0.47 (PE:EA = 15:1). IR (KBr) ν 3068, 1656, 1606, 1588, 1564, 1484, 1454, 1226, 1170, 753, 733, 688 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H), 7.77−7.73 (m, 2H), 7.55−7.53 (m, 3H), 7.48−7.45 (m, 1H), 7.31−7.25 (m, 3H), 7.16 (d, J = 8.25 Hz, 1H), 7.04 (t, J = 7.36 Hz, 1H), 6.86 (d, J = 4.62 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.1, 153.8, 146.3, 145.2, 139.3, 138.2, 133.4, 133.0, 131.2, 130.8, 130.6, 130.4, 130.3, 129.1, 127.7, 124.9, 124.7, 124.5, 122.8, 119.2, 115.9; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{22}H_{15}NO_2Cl$, 360.0791, found 360.0789.

*(Z)-(3-Chlorophenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone (**3p**).* Isolated yield 57 mg (79%); yellow solid; mp 115−117 °C; R_f 0.45 (PE:EA = 15:1). IR (KBr) ν 3057, 1664, 1632, 1600, 1578, 1452, 1263, 1186, 1097, 802, 760, 751, 711, 689 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.05 (d, J = 7.50 Hz, 2H), 7.89 (s, 1H), 7.69−7.66 (m, 2H), 7.57−7.52 (m, 3H), 7.33−7.29 (m, 2H), 7.19 (d, J = 8.20 Hz, 1H), 7.11 (d, J = 7.95 Hz, 1H), 7.06 (s, 1H), 6.95 (d, J = 7.95 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.9, 153.2, 148.5, 147.3, 136.8, 134.2, 133.4, 132.6, 131.2, 130.7, 129.9, 129.4, 129.1, 124.9, 124.1, 122.3, 121.4, 119.2, 116.0; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{22}H_{15}NO_2Cl$, 360.0791, found 360.0796.

*(Z)-(5-Methoxy-2-(phenylimino)-2H-chromen-3-yl)(phenyl)-methanone (**3s**).* Isolated yield 68 mg (96%); yellow solid; mp 185−187 °C; R_f 0.40 (PE:EA = 15:1). IR (KBr) ν 3075, 2997, 2924, 2841, 1668, 1648, 1601, 1587, 1488, 1474, 1284, 1272, 1232, 1189, 1100, 785, 762, 717, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 7.60 Hz, 2H), 7.83 (s, 1H), 7.57 (t, J = 7.30 Hz, 1H), 7.46 (t, J = 7.60 Hz, 2H), 7.32 (t, J = 8.38 Hz, 1H), 7.26−7.25 (m, 2H), 7.06−7.46 (m, 3H), 6.69 (d, J = 8.30 Hz, 1H), 6.63 (d, J = 8.25 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.4, 156.5, 154.4, 146.7, 145.3, 136.6, 133.3, 132.1, 130.7, 129.9, 129.6, 128.4, 128.3, 124.0, 122.8, 109.2, 108.2, 105.2, 55.9; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{23}H_{18}NO_3$, 356.1281, found 356.1290.

*(Z)-(5-Methyl-2-(phenylimino)-2H-chromen-3-yl)(phenyl)-methanone and (Z)-(8-Methyl-2- (phenylimino)-2H-chromen-3-yl)(phenyl)methanone (**3t**).* Isolated yield 52 mg (77%); yellow solid; R_f 0.42 (PE:EA = 15:1). The indicated compounds were obtained as a 0.21:0.79 mixture. IR (KBr) ν 3060, 2925, 1652, 1588, 1557, 1499, 1466, 1295, 1262, 1235, 1182, 757, 732, 710, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 7.55 Hz, 2.3H), 7.61 (s, 0.2H), 7.55 (t, J = 7.38 Hz, 1.2H), 7.44 (t, J = 7.68 Hz, 2.5H), 7.38 (s, 1H), 7.25−7.22 (m, 3.7H), 7.18 (d, J = 7.45 Hz, 1H), 7.07 (d, J = 8.26 Hz, 2.2H), 7.03 (d, J = 7.55 Hz, 2H), 7.01 (s, 0.5H), 6.97 (d, J = 7.32 Hz, 0.3H), 6.91 (d, J = 7.32 Hz, 0.2H), 2.43 (s, 0.8H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 193.3, 154.0, 151.7, 147.1, 146.8, 145.3, 136.5, 135.7, 133.4, 133.1, 132.4, 131.6, 131.3, 129.6, 128.4, 126.0, 125.5, 125.4, 124.1, 123.6, 122.9, 118.5, 117.6, 113.8, 18.3, 15.2; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{23}H_{18}NO_2$, 340.1338, found 340.1341.

*(Z)-(7-Methyl-2-(phenylimino)-2H-chromen-3-yl)(phenyl)-methanone and (Z)-(6-Methyl-2- (phenylimino)-2H-chromen-3-yl)(phenyl)methanone (**3u**).* Isolated yield 50 mg (74%); yellow solid; R_f 0.40 (PE:EA = 15:1). The indicated compounds were obtained as a 0.46:0.54 mixture; IR (KBr) ν 3059, 2924, 1651, 1612, 1590, 1578, 1485, 1247, 1225, 1181, 1134, 1101, 817, 759, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 2H), 8.03 (s, 2H), 7.61 (t, J = 7.33 Hz, 2H), 7.49 (t, J = 7.60 Hz, 4H), 7.44 (s, 1H), 7.40 (s, 1H), 7.31−7.29 (m, 3H), 7.24 (d, J = 7.90 Hz, 1H), 7.19 (s, 1H), 7.09−7.06 (m, 6H), 7.02 (t, J = 6.8 Hz, 2H), 6.95 (s, 1H), 2.41 (s, 3H), 2.38 (s, 2.5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 153.7, 151.7, 147.0, 145.4, 143.0, 136.7, 136.6, 135.5, 135.2, 133.7, 133.3, 132.5, 132.1,131.0, 129.6, 128.4, 128.0, 125.1, 124.1, 122.9, 122.8, 118.7, 116.5, 116.3, 115.6, 21.6, 20.6; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{23}H_{18}NO_2$, 340.1338, found 340.1342.

*(Z)-N-Phenyl-2-(phenylimino)-2H-chromene-3-carboxamide (**4a**).* Isolated yield 55 mg (81%); yellow solid; mp 256−258 °C; R_f 0.50 (PE:EA = 4:1). IR (KBr) ν 3061, 3029, 1681, 1640, 1599, 1589, 1567, 1485, 1222, 1163, 766, 751, 689 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.74 (s, 1H), 8.70 (s, 1H), 7.76 (d, J = 7.80 Hz, 2H), 7.58 (d, J = 7.45 Hz, 1H), 7.52−7.45 (m, 3H), 7.40−7.37 (m, 4H), 7.27−7.23 (m, 2H), 7.17−7.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 153.4, 149.3, 143.8, 141.8, 138.4, 132.9, 129.5, 129.0, 129.0, 125.0, 124.6, 124.4, 123.3, 121.4, 120.4, 119.1, 115.6; HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{22}H_{17}N_2O_2$, 341.1290, found 341.1285.

*(Z)-N-Benzyl-2-(phenylimino)-2H-chromene-3-carboxamide (**4b**).* Isolated yield 55 mg (78%); yellow solid; mp 154−156 °C; R_f 0.46 (PE:EA = 4:1). IR (KBr) ν 3165, 3057, 2927, 2866, 1677, 1635, 1584, 1542,1484, 1451, 1234, 1164, 776, 755, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.81 (s, 1H), 8.63 (s, 1H), 7.54 (d, J = 7.55 Hz, 1H), 7.46 (t, J = 7.72 Hz, 1H), 7.42−7.36 (m, 6H), 7.30 (d, J = 7.10 Hz, 1H), 7.25−7.17 (m, 4H), 7.10 (d, J = 8.20 Hz, 1H), 4.71 (d, J = 5.49 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.2, 153.4, 148.9, 144.1, 141.4, 138.4, 132.6, 129.3, 128.8, 128.6, 127.5, 127.2, 124.6, 124.4, 123.1, 121.2, 119.0, 115.4, 43.8. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{23}H_{19}N_2O_2$, 355.1447, found 355.1440.

*(Z)-2-(Phenylimino)-N-(pyridin-2-yl)-2H-chromene-3-carboxamide (**4c**).* Isolated yield 54 mg (79%); yellow solid; mp 260−262 °C; R_f 0.49 (PE:EA = 4:1). IR (KBr) ν 3062, 1680, 1651, 1604, 1595, 1544, 1485, 1436, 1306, 1236, 1199, 761, 738, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.06 (s, 1H), 8.66 (s, 1H), 8.38−8.37 (m, 2H), 7.74 (t, J = 8.44 Hz, 1H), 7.56 (d, J = 7.40 Hz, 1H), 7.48 (t, J = 7.75 Hz, 1H), 7.42 (d, J = 4.30 Hz, 4H), 7.24−7.19 (m, 2H), 7.14 (d, J = 8.25 Hz, 1H), 7.05(t, J = 6.13 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 153.5, 152.8, 151.8, 148.4, 143.8, 142.1, 138.0, 133.0, 129.5, 128.8, 124.9, 124.6, 123.5, 121.1, 119.8, 118.9, 115.6, 114.9. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{21}H_{16}N_3O_2$, 342.1243, found 342.1245.

*(Z)-5-Methoxy-N-phenyl-2-(phenylimino)-2H-chromene-3-carboxamide (**4d**).* Isolated yield 67 mg (91%); yellow solid; mp 215−217 °C; R_f 0.44 (PE:EA = 4:1). IR (KBr) ν 3066, 3019, 2964, 1675, 1639, 1595, 1558, 1488, 1260, 1200, 1103, 789, 768, 750, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.70 (s, 1H), 9.03 (s, 1H), 7.75 (d, J = 8.10 Hz, 2H), 7.44−7.40 (m, 2H), 7.38−7.34 (m, 5H), 7.20 (t, J = 7.30 Hz, 1H), 7.12 (t, J = 7.32 Hz, 1H), 6.71 (d, J = 8.54 Hz, 1H), 6.67 (d, J = 8.30 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 157.2, 154.1, 149.3, 143.9, 138.5, 137.2, 133.5, 129.0, 128.9, 124.8, 124.1, 123.3, 120.2, 119.3, 109.7, 107.7, 105.5, 56.0. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{23}H_{19}N_2O_3$, 371.13902, found 371.13895.

*(Z)-N-Benzyl-5-methoxy-2-(phenylimino)-2H-chromene-3-carboxamide (**4e**).* Isolated yield 60 mg (78%); yellow solid; mp 165−167 °C; R_f 0.49 (PE:EA = 4:1). IR (KBr) ν 3179, 3054, 2931, 1671, 1632, 1580, 1542, 1488, 1480, 1230, 1102, 774, 734, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.78 (s, 1H), 8.96 (s, 1H), 7.41−7.40 (m, 2H), 7.38−7.34 (m, 5H), 7.28 (t, J = 6.95 Hz, 1H), 7.20 (d, J = 7.75 Hz, 2H), 7.16 (t, J = 7.32 Hz, 1H), 6.65 (t, J = 9.17 Hz, 2H), 4.69 (d, J = 6.14 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 157.1, 154.0, 148.9, 144.2, 138.5, 136.8, 133.1, 128.7, 128.6, 127.5, 127.1, 124.4, 123.1, 119.1, 109.5, 107.6, 105.3, 55.9, 43.7. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{24}H_{21}N_2O_3$, 385.15467, found 385.15469.

*(Z)-5-Methyl-N-phenyl-2-(phenylimino)-2H-chromene-3-carboxamide and (Z)-8-Methyl-N- phenyl-2-(phenylimino)-2H-chromene-3-carboxamide (**4f**).* Isolated yield 63 mg (89%); yellow solid; R_f 0.45 (PE:EA = 4:1). The indicated compounds were obtained as a 0.32:0.68 mixture. IR (KBr) ν 3056, 3026, 2976, 1680, 1638, 1598, 1559, 1499, 1487, 1320, 1263, 1221, 1203, 1159, 781, 768, 749, 687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.80 (s, 0.5H), 12.74 (s, 1H), 8.88 (s, 0.5H), 8.64 (s, 1H), 7.75 (d, J = 7.80 Hz, 3H), 7.43 (t, J = 7.75 Hz, 3H), 7.39−7.35 (m, 7H), 7.31 (t, J = 6.70 Hz, 1.5H), 7.21 (t, J = 7.30 Hz, 1.5H), 7.13 (t, J = 7.93 Hz, 2.5H), 7.06 (d, J = 7.40 Hz, 0.5H), 6.96 (d, J = 8.30 Hz, 0.5H), 2.59 (s, 1.5H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 160.0, 153.8, 151.6, 149.6, 149.2, 144.0, 142.2, 138.9, 138.3, 138.1, 134.3, 132.5, 129.0, 128.8, 127.2, 125.9, 125.2, 124.9, 124.3, 124.2, 123.3, 123.1, 120.8, 120.3, 118.7, 117.8, 113.4, 18.4, 15.2. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{23}H_{19}N_2O_2$, 355.14410, found 355.14413.

DOI: 10.1021/acs.joc.6b00843
J. Org. Chem. 2016, 81, 5942−5948

*(Z)-N-Benzyl-5-methyl-2-(phenylimino)-2H-chromene-3-carboxamide and (Z)-N-Benzyl-8- methyl-2-(phenylimino)-2H-chromene-3-carboxamide (**4g**).* Isolated yield 66 mg (90%); yellow solid; R_f 0.47 (PE:EA = 4:1). The indicated compounds were obtained as a 0.28:0.72 mixture. IR (KBr) ν 3181, 3056, 3030, 2927, 1671, 1636, 1589, 1545, 1487, 1456, 1237, 1204, 1174, 1074, 768, 758, 740, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 10.85 (s, 0.4H), 10.8 (s, 1H), 8.82 (s, 0.4H), 8.58 (s, 1H), 7.39 (t, J = 5.68 Hz, 3H), 7.36−7.33 (m, 6H), 7.31 (s, 0.4H), 7.28−7.25 (m, 2.6H), 7.22−7.19 (m, 3H), 7.16−7.13 (m, 1.2H), 7.10 (t, J = 7.73 Hz, 1H), 7.03 (d, J = 7.90 Hz, 0.4H), 6.91 (d, J = 8.55 Hz, 0.4H), 4.70 (s, 0.80H), 4.68 (s, 2H), 2.56 (s, 1.17H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 162.4, 153.8, 151.5, 149.3, 144.3, 141.9, 138.5, 138.4, 137.9, 134.0, 132.3, 128.6, 127.5, 127.2, 127.0, 125.7, 125.1, 124.5, 124.0, 123.1, 123.0, 120.6, 120.2, 118.6, 113.3, 43.8, 18.3, 15.1. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{24}H_{21}N_2O_2$, 369.15975, found 369.15976.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00843.

X-ray data for **3a** in CIF format (CIF)

^1H, ^{13}C and ^{19}F NMR spectra of all new compounds. Table of crystal data and structure refinement for **3a** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liming928@qust.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (21372137 and 21572110) and the Natural Science Foundation of Shandong Province (ZR2014BM006).

■ REFERENCES

(1) (a) Endo, S.; Hu, D.-W.; Suyama, M.; Matsunaga, T.; Sugimoto, K.; Matsuya, Y.; El-Kabbani, O.; Kuwata, K.; Hara, A.; Kitade, Y.; Toyooka, N. *Bioorg. Med. Chem.* **2013**, *21*, 6378−6384. (b) Endo, S.; Matsunaga, T.; Kuwata, K.; Zhao, H.-T.; El-Kabbani, O.; Kitade, Y.; Hara, A. *Bioorg. Med. Chem.* **2010**, *18*, 2485−2490.

(2) Edraki, N.; Firuzi, O.; Foroumadi, A.; Miri, R.; Madadkar-Sobhani, A.; Khoshneviszadeh, M.; Shafiee, A. *Bioorg. Med. Chem.* **2013**, *21*, 2396−2412.

(3) Guo, D.-L.; Chen, T.; Ye, D.-J.; Xu, J.-Y.; Jiang, H.-L.; Chen, K.-X.; Wang, H.; Liu, H. *Org. Lett.* **2011**, *13*, 2884−2887.

(4) (a) Rajagopal, R.; Seshadri, S. *Dyes Pigm.* **1990**, *13*, 29−44. (b) Gorobets, N. Y.; Yousefi, B. H.; Belaj, F.; Kappe, C. O. *Tetrahedron* **2004**, *60*, 8633−8644. (c) Borisov, A. V.; Dzhavakhishvili, S. G.; Zhuravel, I. O.; Kovalenko, S. M.; Nikitchenko, V. M. *J. Comb. Chem.* **2007**, *9*, 5−8. (d) Proenc-a, F.; Costa, M. *Green Chem.* **2008**, *10*, 995−998.

(5) (a) Zhang, L.; Dong, J.-H.; Xu, X.-X.; Liu, Q. *Chem. Rev.* **2016**, *116*, 287−322. (b) Jagodziński, T. S. *Chem. Rev.* **2003**, *103*, 197−228. (c) Ila, H.; Junjappa, H. *Chimia* **2013**, *67*, 17−22. (d) Guo, W.-S.; Wen, L.-R.; Li, M. *Org. Biomol. Chem.* **2015**, *13*, 1942−1953. (e) Venkatesh, C.; Singh, B.; Mahata, P. K.; Ila, H.; Junjappa, H. *Org. Lett.* **2005**, *7*, 2169−2172. (f) Zhao, Y.; Zhang, W.; Wang, S.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 4985−4988. (g) Kumar, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 7046−7051. (h) Luo, H.; Pan, L.; Xu, X.; Liu, Q. *J. Org. Chem.* **2015**, *80*, 8282−8289. (i) Xu, C.; Liu, J.; Ming, W.; Liu, Y.; Liu, J.; Wang, M.; Liu, Q. *Chem. - Eur. J.* **2013**, *19*, 9104−9109.

(6) (a) Singh, M. S.; Nandi, G. C.; Samai, S. *Green Chem.* **2012**, *14*, 447−455. (b) Verma, G. K.; Shukla, G.; Nagaraju, A.; Srivastava, A.; Raghuvanshi, K.; Singh, M. S. *RSC Adv.* **2014**, *4*, 11640−11647. (c) Huang, F.; Wu, P.; Wang, L.; Chen, J.; Sun, C.; Yu, Z. *Chem. Commun.* **2014**, *50*, 12479−12481. (d) Huang, F.; Wu, P.; Wang, L.; Chen, J.; Sun, C.; Yu, Z. *J. Org. Chem.* **2014**, *79*, 10553−10560. (e) Srivastava, A.; Shukla, G.; Nagaraju, A.; Verma, G. K.; Raghuvanshi, K.; Jones, R. C. F.; Singh, M. S. *Org. Biomol. Chem.* **2014**, *12*, 5484−5491. (f) Wang, Z.-L.; Li, H.-L.; Ge, L.-S.; An, X.-L.; Zhang, Z.-G.; Luo, X.-Y.; Fossey, J. S.; Deng, W.-P. *J. Org. Chem.* **2014**, *79*, 1156−1165. (g) Luo, X.-Y.; Ge, L.-S.; An, X.-L.; Jin, J.-H.; Wang, Y.; Sun, P.-P.; Deng, W.-P. *J. Org. Chem.* **2015**, *80*, 4611−4617.

(7) (a) Bhunia, A.; Reddy Yetra, S.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140−3152. (b) Dong, Y.; Liu, B.-Y.; Chen, P.; Liu, Q.; Wang, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3442−3446. (c) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701−730. (d) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191−218. (e) Wu, C.-R.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116−125. (f) Worlikar, S. A.; Larock, R. C. *Curr. Org. Chem.* **2011**, *15*, 3214−3232. (g) Yoshida, S.; Yano, T.; Misawa, Y.; Sugimura, Y.; Igawa, K.; Shimizu, S.; Tomooka, K.; Hosoya, T. *J. Am. Chem. Soc.* **2015**, *137*, 14071−14074. (h) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798−15805.

(8) (a) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458−3461. (b) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4488−4491. (c) Bhunia, A.; Porwal, D.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2013**, *15*, 4620−4623. (d) Bunescu, A.; Wang, Q.; Zhu, J.-P. *Org. Lett.* **2014**, *16*, 1756−1759. (e) Liu, F.-L.; Yang, H.-M.; Hu, X.-Q.; Jiang, G.-X. *Org. Lett.* **2014**, *16*, 6408−6411. (f) Roy, T.; Bhojgude, S. S.; Kaicharla, T.; Thangaraj, M.; Garai, B.; Biju, A. T. *Org. Chem. Front.* **2016**, *3*, 71−76. (g) Yoshida, H.; Ito, Y.; Ohshita, J. *Chem. Commun.* **2011**, *47*, 8512−8514.

(9) (a) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638−6642. (b) Yoshioka, E.; Tanaka, H.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2013**, *15*, 3938−3941. (c) Yoshioka, E.; Nishimura, M.; Nakazawa, T.; Kohtani, S.; Miyabe, H. *J. Org. Chem.* **2015**, *80*, 8464−8469. (d) Yoshioka, E.; Tamenaga, H.; Miyabe, H. *Tetrahedron Lett.* **2014**, *55*, 1402−1405.

(10) (a) Li, M.; Kong, X.-J.; Wen, L.-R. *J. Org. Chem.* **2015**, *80*, 11999−12005. (b) Wen, L.-R.; Men, L.-B.; He, T.; Ji, G.-J.; Li, M. *Chem. - Eur. J.* **2014**, *20*, 5028−5033. (c) Wen, L.-R.; Jin, X.-J.; Niu, X.-D.; Li, M. *J. Org. Chem.* **2015**, *80*, 90−98. (d) Li, M.; Cao, H.; Wang, Y.; Lv, X.-L.; Wen, L.-R. *Org. Lett.* **2012**, *14*, 3470−3473. (e) Wen, L.-R.; He, T.; Lan, M.-C.; Li, M. *J. Org. Chem.* **2013**, *78*, 10617−10628. (f) Wen, L.-R.; Shi, Y.-J.; Liu, G.-Y.; Li, M. *J. Org. Chem.* **2012**, *77*, 4252−4260. (g) Li, M.; Hou, Y.-L.; Wen, L.-R.; Gong, F.-M. *J. Org. Chem.* **2010**, *75*, 8522−8532.

(11) Feng, X.; Wang, J.-J.; Xun, Z.; Huang, Z.-B.; Shi, D.-Q. *J. Org. Chem.* **2015**, *80*, 1025−1033.

(12) Huang, P.; Xiang, D.-X.; Zhou, Y.; Liang, Y.-J.; Na, T.-H.; Dong, D.-W. *Synthesis* **2009**, *11*, 1797−1800.

DOI: 10.1021/acs.joc.6b00843
J. Org. Chem. 2016, 81, 5942−5948