JOC The Journal of Organic Chemistry

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Metal-Free One-Pot Annulative Coupling of 2-Hydroxybenzaldehydes with β-Ketothioamides: Access to Diverse 2-Arylimino-2*H*-Chromenes

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Cite This: *J. Org. Chem.* 2022, 87, 12342−12351 Read Online

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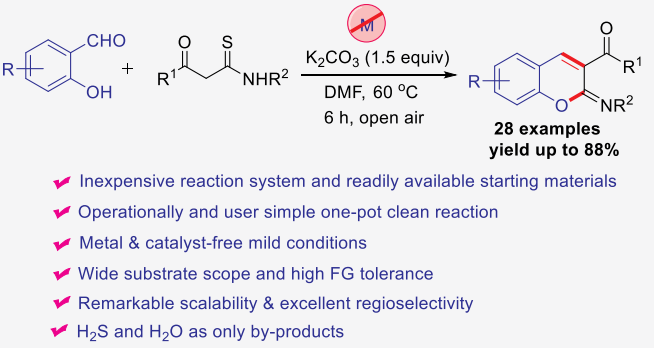
ABSTRACT: A concise and practical one-pot sustainable approach for expedient synthesis of 2-arylimino-2*H*-chromenes by two-component cascade [4 + 2] annulative coupling of easily available 2-hydroxybenzaldehydes with β-ketothioamides has been developed in good yields for the first time. Remarkably, metal- and additive-free conditions, use of simple K_2CO_3 as a mild base, open atmosphere, exclusive regioselectivity, step/atom economy, non-hazardous reagents, and easy purification are added characteristics to the strategy. This annulative protocol will not only provide an efficient method to access diverse chromene scaffolds, but also enrich the research domain of β-ketothioamides.



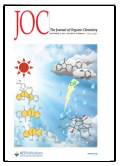
INTRODUCTION

H-Chromenes (2*H*-1-benzopyran derivatives) represent one of the important classes of oxygen heterocycles and have attracted significant attention owing to their extensive existence as a core skeleton in several natural products,[1] biologically pertinent molecules,[2] and photochromic materials.[3] Further, substituted chromenes also play a key role in the regulation of various biopolymers.[4] For instance, compounds such as *N*-(2*H*-chromen-2-ylidene)arylamines are explored as inhibitors of aldo-keto reductase (AKR) 1B10[2a] as therapeutics for the management of cancer and inhibitors of β-secretase (BACE1)[2b] for the treatment of Alzheimer's disease (Figure 1). The natural product candenatenin E (**I**) exhibits potent cancer cell cytotoxicity,[5a5b] and synthetic compound **III** processes anti-inflammatory activity, which has been employed as a TNF-α inhibitor.[5c] Additionally, some chromene derivatives act as being cell membrane permeable with low cytotoxicity and able to selectively stain organelles in living cells.[6a] 2*H*-Chromene analogues have also found applications in photochromic materials[6b] (Figure 1).

Literature reports for the construction of 2*H*-chromene derivatives generally comprise benzopyran-ring formation strategies involving intramolecular annulations of 2-substituted hydroxy-protected phenol derivatives and intermolecular organo- or metal-catalyzed/mediated cyclization/annulation reactions.[7] Recently, synthesis of 2*H*-chromenes via benzopyran ring formation via cyclization reactions has been reviewed by Zheng and Chen.[8] However, most of the reported approaches relied on chlorinated solvents, harsh conditions, cumbersome workup procedures, and either a limited variety of available starting materials or the use of expensive catalysts.[9] Traditionally, salicylaldehyde has been utilized as a reaction partner for the synthesis of 2-aryliminochromenes via stepwise reactions[6a] (Scheme 1a). Li and co-workers[10] performed the reaction of 2-trimethylsilylphenyl triflate (Kobayashi precursor) and β-ketothioamide in 2:1 molar ratio in dimethylformamide (DMF) in the presence of potassium fluoride (Scheme 1b). Work up of the reaction provided the desired product 3-benzoyl-2-phenyliminochromene in 12% yield together with S-phenylated β-ketothioamide in 53% yield as a major product. Next, the same group employed N,S-ketene acetals in place of thioamide, which resulted in the desired 2-aryliminochromenes in high yield. However, the above one-pot reaction required a costly Kobayashi precursor, high temperature (90 °C), and reaction time up to 25 h. Consequently, it would be significant to develop proficient methodologies for the synthesis of 2-arylimino-2*H*-chromene derivatives from easily viable substrates under mild conditions to meet increasing organic and pharmaceutical research demand.

In spite of the fact that chromenes have been discovered much earlier, they have gained much less considerable attention in advancing further development. Therefore, the development of an efficient, more general approach that

Received: July 7, 2022
Revised: August 19, 2022
Accepted: August 25, 2022
Published: August 29, 2022



https://doi.org/10.1021/acs.joc.2c01581
J. Org. Chem. 2022, 87, 12342−12351

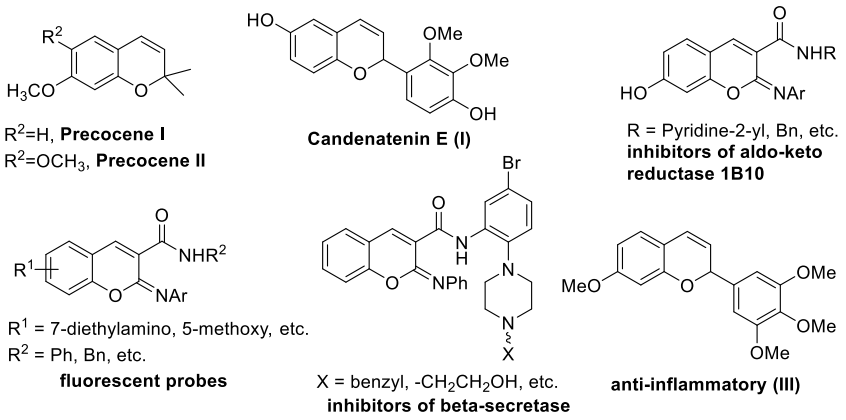
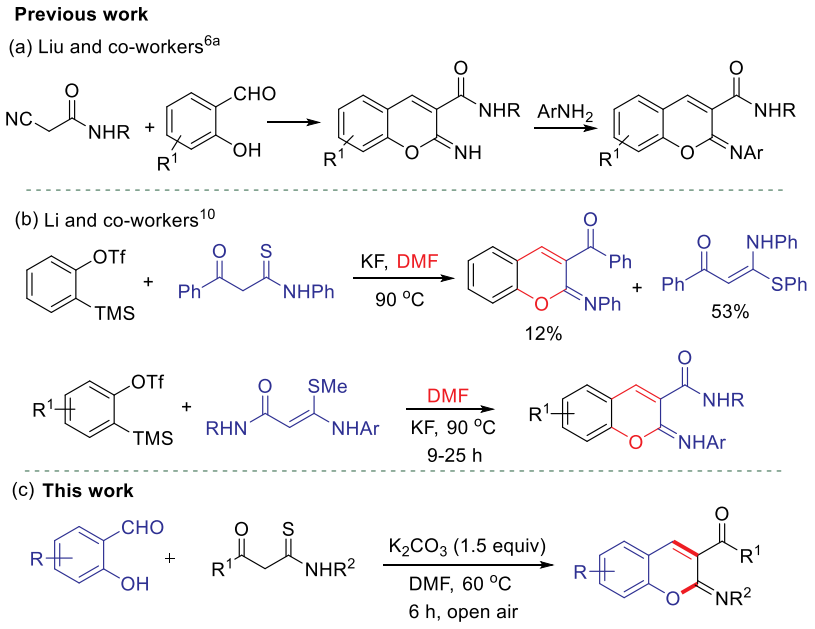
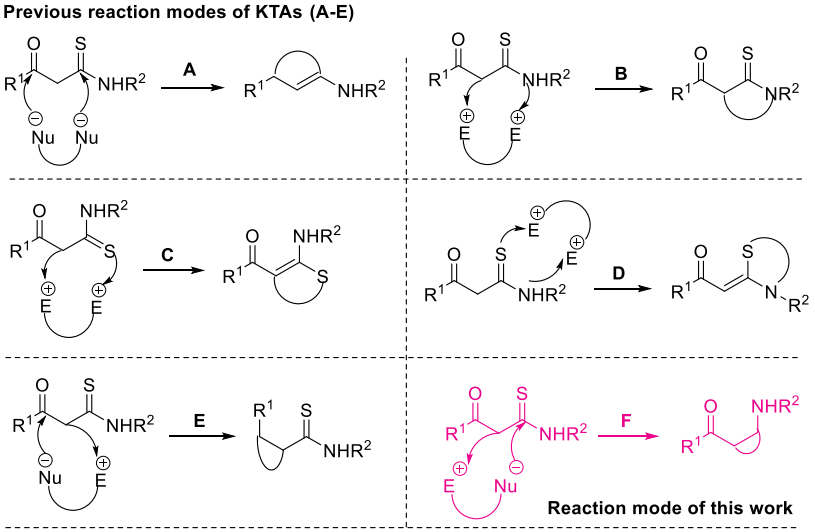


Figure 1. Representative examples of some natural products and biologically active molecules bearing a 2*H*-chromene framework.

Scheme 1. Synthesis of 2-Arylimino-2*H*-Chromenes



Scheme 2. Structural Features and Reaction Modes of KTAs



enables direct access to 2-arylimino-2*H*-chromene derivatives from simple precursors is much awaited. In this context, we reveal the first quantitative one-pot metal- and additive-free synthesis of 2-arylimino-2*H*-chromenes from readily available

https://doi.org/10.1021/acs.joc.2c01581
J. Org. Chem. 2022, 87, 12342−12351

salicylaldehydes and β-ketothioamides (KTAs) in the presence of mild base K_2CO_3 (Scheme 1c). To the best of our knowledge, no direct approach to construct 2-arylimino-2*H*-chromene employing salicylaldehyde and β-ketothioamide has been reported so far. This strategy would broaden the chemistry of β-ketothioamide and hold great potential in the concise synthesis of valuable molecules. The method is step, pot, and carbon economic, metal-free, devoid of toxic reagents, and has a wide substrate scope.

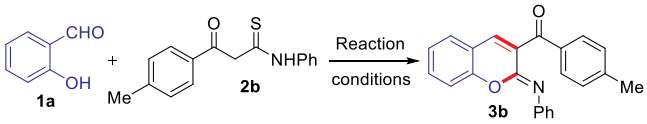
The demand for better synthetic methods toward bioactive heterocyclic scaffolds and their derivatives is high and continuous. The efficient and selective synthesis of functionalized 2*H*-chromenes remains an important pursuit within synthetic organic chemistry.[7−10] The metal-free cyclization reactions of acyclic precursors in which a benzopyran ring is generated are fascinating and step-economical routes to 2*H*-chromenes. β-Ketothioamides proved to be attractive and versatile synthons and are arguably referred to as "privileged scaffolds" within the synthetic community, due to their ease of preparation, ready diversification, and faceted reactivity. The previous reports of KTAs participating in reactions mainly involved five types (Scheme 2, modes A−E). The inherent synthetic tunability and stimulating chemistry of KTAs in various synthetic transformations has been brought out in the recent past.[11] Over the past years, reactions of β-ketothioamides with a variety of electrophiles have been carried out to construct important heterocycles.[12] Despite the synthesis of different nitrogen- and sulfur-containing heterocycles from β-ketothioamides, the synthesis of oxygen-containing heterocycles are very much limited.[13] In continuation of our interests in the utilization of KTAs,[11,12] we envisioned to utilize β-ketothioamides for the construction of oxygen heterocycles. Although numerous methods for the synthesis of 2*H*-chromenes employing various synthons have been developed, protocols directed to utilize β-ketothioamide remain limited.

RESULTS AND DISCUSSION

To begin with, the reaction of salicylaldehyde (**1a**, 0.50 mmol) and β-ketothioamide (**2b**, 0.50 mmol) in the presence of K_2CO_3 (0.5 equiv) in 2.0 mL of dimethyl formamide (DMF) at room temperature under an open atmosphere was carried out. The reaction did not proceed at all even after 24 h of vigorous stirring, and the starting material remained completely unreacted (Table 1, entry 1). In an effort to trigger the reaction, the above test reaction was performed at higher temperature of 40 and 60 °C, separately under similar conditions (Table 1, entries 2 and 3). Gratifyingly, the desired product **3b** was obtained in 70% yield within 6 h at 60 °C (Table 1, entry 3). Motivated by the above observations, we focused on exploring the optimal reaction conditions for the synthesis of compound **3b**. Further, reaction at higher temperature could not provide the better result (Table 1, entry 4). Hence, 60 °C was found to be an optimized temperature for the reaction. After optimizing the temperature of the reaction, next the amount of K_2CO_3 was investigated (Table 1, entries 5−7).

It was found that 1.5 equiv of K_2CO_3 provided the target product **3b** in 82% yield within 6 h (Table 1, entry 6). Further increasing the amount of K_2CO_3 to 2.0 equiv could not improve the yield of **3b** (Table 1, entry 7). In order to check the effect of solvent on the reaction, various polar aprotic, polar protic, and nonpolar solvents such as DCE, THF, ACN, DMA

Table 1. Optimization of Reaction Conditions[a]



entry	solvent (3 mL)	base (equiv)	temp (°C)	time (h)	yield (%)[b]
1	DMF	K_2CO_3 (0.5)	rt	24	nr
2	DMF	K_2CO_3 (0.5)	40	10	46
3	DMF	K_2CO_3 (0.5)	60	6	70
4	DMF	K_2CO_3 (0.5)	80	6	58
5	DMF	K_2CO_3 (1.0)	60	10	76
6	DMF	K_2CO_3 (1.5)	60	6	82
7	DMF	K_2CO_3 (2.0)	60	6	82
8	DCE	K_2CO_3 (1.5)	60	6	44
9	THF	K_2CO_3 (1.5)	60	6	38
10	ACN	K_2CO_3 (1.5)	60	6	55
11	DMA	K_2CO_3 (1.5)	60	6	77
12	MeOH	K_2CO_3 (1.5)	60	6	32
13	EtOH	K_2CO_3 (1.5)	60	6	14
14	Toluene	K_2CO_3 (1.5)	60	6	nr
15	DMF	Na_2CO_3 (1.5)	60	6	58
16	DMF	Cs_2CO_3 (1.5)	60	6	80
17	DMF	Et_3N	60	6	46
18	DMF	DABCO	60	6	32
19	DMF	DMAP	60	6	61
20	DMF	none	60	24	nr
21	none	K_2CO_3 (1.5)	60	24	42
22	none	K_2CO_3 (1.5)	80	24	58

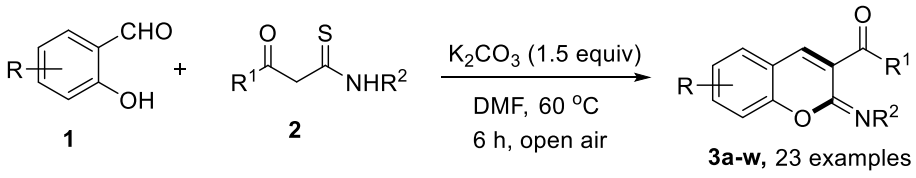
[a]Reactions were performed with 0.50 mmol scale under an open atmosphere. [b]Isolated yield. nr = no reaction.

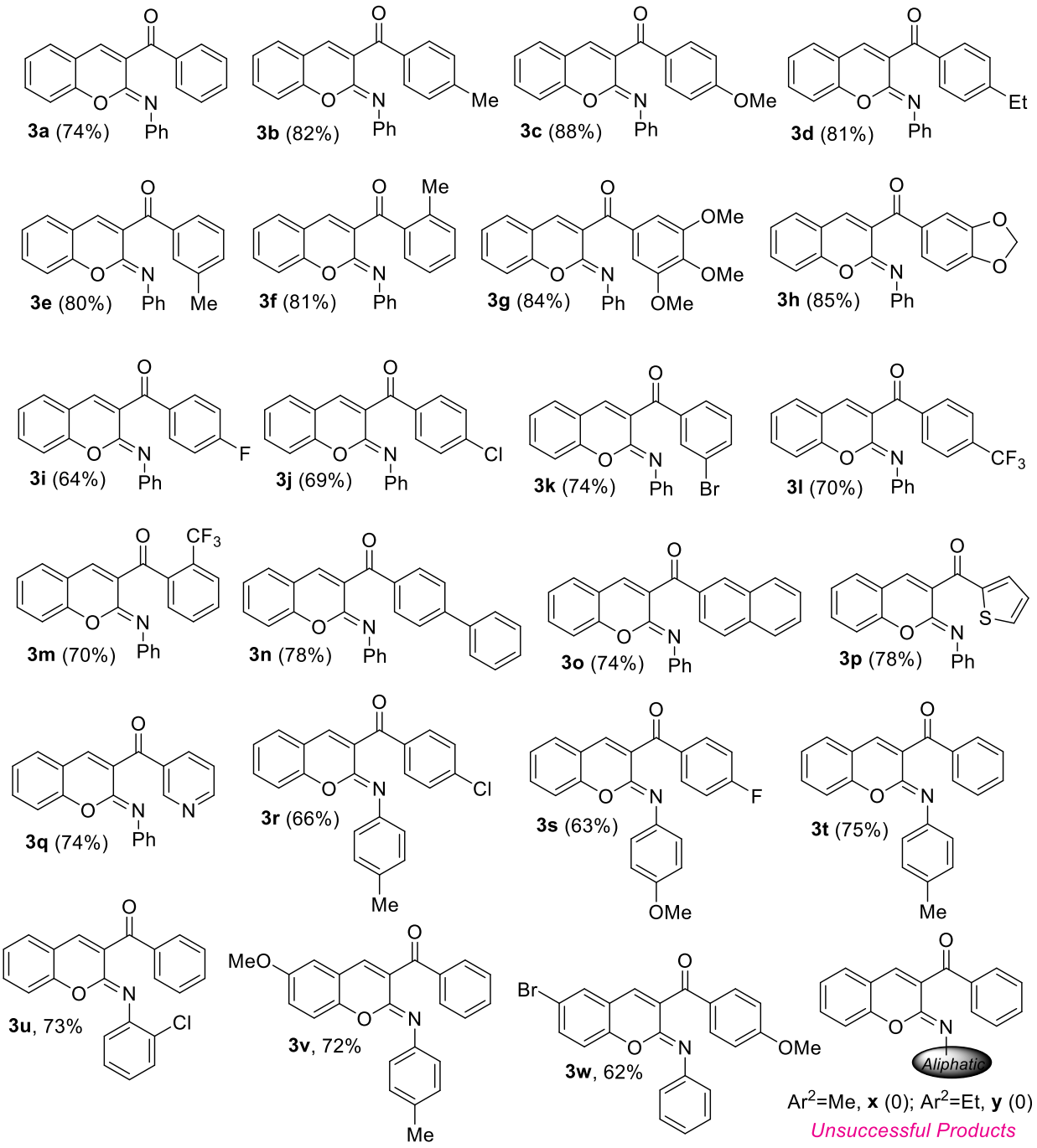
(*N*,*N*-dimethylacetamide), MeOH, EtOH, and toluene were evaluated (Table 1, entries 8−14). None of the above screened solvents were found to be better than DMF, exhibiting DMF as a best choice of solvent for this annulative reaction. Next, different inorganic and organic bases such as Na_2CO_3, Cs_2CO_3, Et_3N, DABCO (1,4-diazabicyclo[2.2.2]octane), and DMAP (4-(dimethylamino)pyridine) were also screened, but none of them was found to be better than K_2CO_3 (Table 1, entries 15−19). A control experiment verified that the reaction does not proceed at all in the absence of base (Table 1, entry 20). Finally, the model reaction of **1a** and **2b** was carried out under solvent-free condition with K_2CO_3 (1.5 equiv) as a base under optimized conditions. It was observed that at 60 °C the desired compound **3b** was obtained in 42% yield, and at 80 °C the yield of the desired compound **3b** was found to be 58% (Table 1, entries 21 and 22). Thus, the best yield, cleanest reaction, and most facile workup was realized by using an equimolar quantity of **1a** (0.5 mmol) and **2b** (0.5 mmol) in the presence of K_2CO_3 (1.5 equiv) in 2.0 mL of DMF at 60 °C in open air (Table 1, entry 6).

After establishing the optimum conditions, we commenced exploring the substrate generality and scope. The outcomes are listed in Table 2. As can be seen, a wide range of β-ketothioamides were well-tolerated, and in all cases the reactions proceeded smoothly to afford the corresponding products **3** in good to high yields. To address the factors that determine the reaction yield and outcome, the electronic and steric effects of various substituents at R^1 and R^2 of β-ketothioamides were tested under the optimal reaction conditions. The R^1 of KTAs with electron-donating groups

https://doi.org/10.1021/acs.joc.2c01581
J. Org. Chem. 2022, 87, 12342−12351

Table 2. Substrate Scope for the Synthesis of 2-Arylimino-2*H*-Chromenes 3[a]





[a]Reaction conditions unless otherwise stated: **1a** (0.5 mmol), **2a** (0.5 mmol), K_2CO_3 (1.5 equiv) in DMF (2.0 mL) at 60 °C in an open atmosphere.

such as Me, OMe, and Et at *ortho*-, *meta*-, and *para*-positions worked well providing the desired products in high yields (Table 2, **3b**−**3f**). The impact of sterically hindered and electron-donating substituents such as 3,4,5-trimethoxyphenyl and 3,4-methylenedioxyphenyl as R^1 was found to be minimal, and proved to be good substrates for the reaction, furnishing the desired products in 84% and 85% yield, respectively (Table 2, **3g** and **3h**). Next, thioamides bearing electron-withdrawing

https://doi.org/10.1021/acs.joc.2c01581
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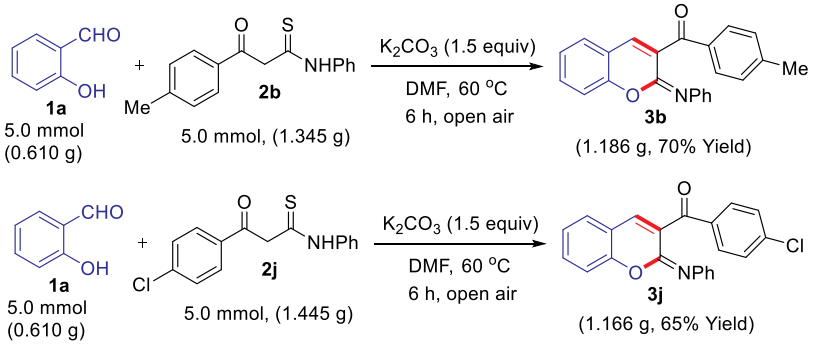
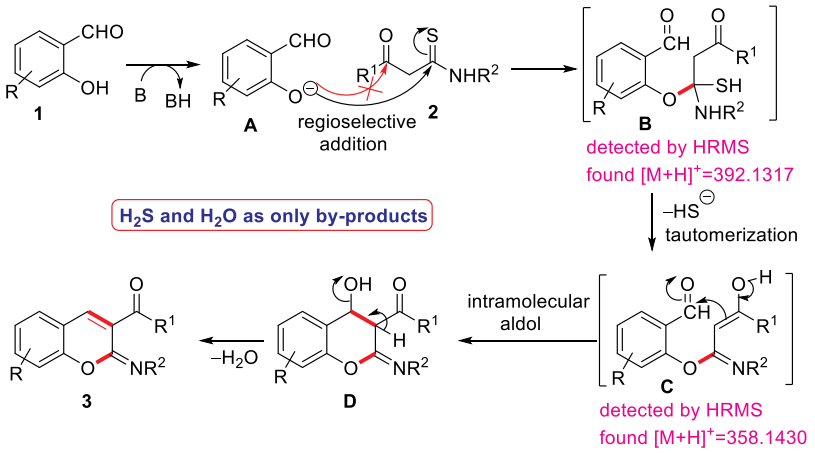
Scheme 3. Large Scale Synthesis of Compounds 3b and 3j



Scheme 4. Plausible Reaction Mechanism



(e.g., F, Cl, Br, and CF_3) groups irrespective of *ortho*-, *meta*-, and *para*-positions reacted smoothly, and provided the corresponding products in good yields (Table 2, **3i**–**3m**). Hence, no obvious electronic effect of substituents on the outcome of the reaction was observed. Moreover, halo-substituted derivatives could be potential precursors for further synthetic manipulations. Notably, *β*-ketothioamides bearing R^1 moiety as extended aromatics (such as biphenyl and naphthyl groups) were also tolerated well under the standard conditions affording the desired products in 78% and 74% yield, respectively (Table 2, **3n**–**3o**). After the successful utilization of R^1 moiety as aromatic and extended aromatics, we envisioned to employ heteroaromatic groups such as 2-thienyl and 3-pyridyl moieties. Importantly, thioamides bearing electron-excessive and electron-deficient groups such as 2-thienyl and 3-pyridyl groups as R^1 were also found to be well compatible under standard conditions, enabling the corresponding products in high yields (Table 2, **3p**–**3q**).

To further enhance the scope of the reaction and to introduce substituent diversity into the product, we evaluated the thioamides bearing different R^2 moieties. KTAs bearing R^2 moieties such as 4-methylphenyl, 4-methoxyphenyl, and 2-chlorophenyl groups also underwent the reaction smoothly affording the corresponding products in good yields (Table 2, **3r**–**3u**). Further to explore the versatility of the reaction, substituted aldehydes such as 2-hydroxy-5-methoxybenzaldehyde and 5-bromo-2-hydroxybenzaldehyde were also investigated under standard conditions. The both above aldehydes reacted well, furnishing the corresponding products in good yields (Table 2, **3v**–**3w**). On the other hand, when the R^2 moiety was switched to an alkyl group such as methyl or ethyl, unfortunately, we could not get our desired products with these substrates. Longer reaction time and raising the temperature led to several overlapping spots on the TLC plate, which could not be isolated, thus limiting the scope of the reaction to some extent (Table 2, **3x**, **3y**).

To check the synthetic efficacy and to demonstrate the practical application of the present protocol, we performed gram scale reaction with KTAs **2b** and **2j** (5.0 mmol each, 1.345 and 1.445 g, respectively) with salicylaldehyde **1a** (5.0 mmol, 0.610 g) under the standard conditions (Scheme 3). The expected products **3b** (1.288 g, 76%) and **3j** (1.166 g, 65%) were found to be comparable with small-scale reactions (Table 2, entries **3b** (82%), **3j** (69%). This result showed that the present method could be easily adopted for a large-scale preparation.

Although the exact mechanism is still unclear, taking into account all of the above observations and entire experimental outcomes into consideration, a plausible mechanistic pathway for the formation of compound **3** is outlined in Scheme 4. The salicylaldehyde **1** reacts with base to generate anionic species **A**, which undergoes regioselective conjugate addition with thioamide **2** to afford adduct **B** (detected by HRMS study). The adduct **B** undergoes sequential elimination of H_2S followed by tautomerization to give intermediate **C** (detected by HRMS study). The intermediate **C** undergoes an intramolecular aldol reaction, giving rise to the bicyclic intermediate **D**, which readily dehydrates, affording the desired 2-arylimino-2*H*-chromene **3**. The overall domino process comprises deprotonation, conjugate addition, elimination/tautomerization, intramolecular aldol cyclization, and a final dehydration step allowing for the manipulation of three

https://doi.org/10.1021/acs.joc.2c01581
J. Org. Chem. 2022, 87, 12342−12351

functional groups. This strategy exploits the electrophilic and nucleophilic dual role of thioamide protocol without involving predecorated substrates or multiple synthetic steps. H_2O and H_2S as the only byproducts lead to sustainability. This mechanistic hypothesis was supported by HRMS studies in which both intermediates **B** and **C** have been detected. It is worth noting here that the carbonyl group of KTAs is as a "pseudo reactive site", and the actual reaction center is involved in the thiocarbonyl group.

The structures of all the synthesized compounds were accomplished by their acceptable spectral (^{1}H, ^{13}C{^{1}H} NMR, and HRMS) studies. Finally, the absolute structure of one of the representative compounds, (*Z*)-(2-(phenylimino)-2*H*-chromen-3-yl)(*o*-tolyl)methanone (**3f**), was unequivocally established by the single crystal X-ray diffraction analysis[14] (Figure 2, see Supporting Information for details).

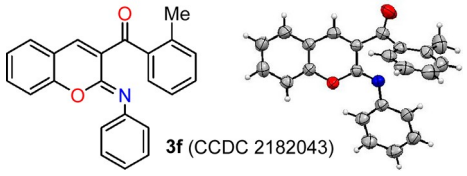


Figure 2. ORTEP diagram of compound **3f** (CCDC 2182043).

In conclusion, a facile metal-free methodology has been established to access 2-arylimino-2*H*-chromenes employing easily viable and cheap salicylaldehydes and *β*-ketothioamides in open air for the first time. The important features of this procedure are moderate conditions, high yield, operational simplicity, step and atom economy, and environmental friendliness. Generation of H_2S and H_2O as the only byproducts makes this 100% carbon-efficient process attractive for the synthesis of 2*H*-chromenes. A variety of unactivated *β*-ketothioamides with a diverse array of substituents, irrespective of their electronic and steric nature, were tolerated well under optimal conditions. The synthetic utility and practicability of this transformation were revealed through gram-scale syntheses. The protocol proceeded smoothly via a route involving the detected reaction intermediates **A** and **B** by HRMS study, and afforded pharmaceutically relevant probes arylimino-2*H*-chromene in good yields.

EXPERIMENTAL SECTION

General Information. The commercially available solvents and reagents were used as received without further purification. The *β*-ketothioamides were synthesized by the reported procedures.[12] *N*,*N*-Dimethylformamide (DMF) was purchased from Merck, and K_2CO_3 was purchased from Sigma-Aldrich. All of the reactions were monitored by analytical thin layer chromatography (TLC) using Merck precoated aluminum sheets and visualized by a UV lamp. Flash column chromatography was performed on silica gel (230−400 mesh). The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 500 FT-NMR spectrometer operating at 500 and 125 MHz, respectively. Chemical shifts (*δ*) for ^{1}H and ^{13}C{^{1}H} NMR are given in parts per million (ppm) using the residual solvent peaks as reference relative to tetramethylsilane (TMS). Coupling constant (*J*) values are reported in Hertz (Hz). High-resolution mass spectra (HRMS, *m*/*z*) were recorded in EI or ESI mode, on a Sciex X500R QTOF instrument. All the reactions were carried out using a single-neck round-bottom (25 mL) borosilicate flask. Melting points have been determined with a Büchi B-540 melting point apparatus and are uncorrected. IUPAC names were obtained using the ChemDraw (version 12.0) software.

General Experimental Procedure for the Synthesis of Compounds 3. Salicylaldehyde **1** (0.5 mmol), *β*-ketothioamide **2** (0.5 mmol), and K_2CO_3 (1.5 equiv) were added into a 25 mL oven-dried single neck round-bottom flask followed by addition of 2 mL of DMF. The reaction mixture was allowed to stir in an oil bath at 60 °C for 6 h in an open atmosphere. After completion of the reaction (monitored by TLC), the reaction was quenched with water (10 mL) followed by extraction with ethyl acetate (15 mL) and water (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude residue thus obtained was purified by silica gel column chromatography to give the pure product **3** (in a mixture of ethyl acetate and hexane in 1:9 ratio). The isolated product was dried under a vacuum, and then the analytical studies were performed.

The spectral and analytical data of all the compounds are given as follows.

*(Z)-Phenyl(2-(phenylimino)-2H-chromen-3-yl)methanone (**3a**).*[10] The product was obtained as a yellow solid (74%, 120 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.90 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.37−7.32 (m, 3H), 7.24−7.22 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.03−7.00 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, CDC_{l3}) *δ* 193.3, 153.7, 146.8, 145.3, 136.6, 135.3, 133.6, 132.3, 131.8, 129.8, 128.6, 128.5, 128.4, 124.3, 124.2, 122.9, 119.1, 116.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{16}NO_2$ 326.1181, found 326.1185.

*(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(p-tolyl)methanone (**3b**).*[10] The product was obtained as a yellow solid (82%, 138 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 164−166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.93 (d, *J* = 8.00 Hz, 2H), 7.41−7.36 (m, 3H), 7.30−7.26 (m, 4H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.10−7.05 (m, 4H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) *δ* 192.9, 153.6, 146.9, 145.4, 144.6, 134.9, 134.0, 132.5, 131.6, 130.0, 129.3, 128.5, 128.3, 124.2, 124.2, 122.9, 119.1, 116.0, 21.9; HRMS (ESI-TOF) *m*/*z* [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 (**3c**).*[10] The product was obtained as a yellow solid (88%, 156 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 157−159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.00 (d, *J* = 8.0 Hz, 2H), 7.39−7.34 (m, 3H), 7.30−7.27 (m, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.10−7.07 (m, 4H), 6.95 (d, *J* = 9.0, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) *δ* 191.7, 164.1, 153.5, 147.0, 145.5, 134.6, 132.5, 132.3, 131.5, 129.5, 129.4, 128.5, 128.2, 124.2, 124.1, 122.9, 119.1, 115.9, 113.8, 55.6; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{18}NO_3$, 356.1287, found 356.1295.

*(Z)-(4-Ethylphenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone (**3d**).* The product was obtained as a yellow sticky solid (81%, 142 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.95 (d, *J* = 8.0 Hz, 2H), 7.40−7.35 (m, 3H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.42−7.37 (m, 3H), 7.29−7.26 (m, 2H), 7.29−7.24 (m, 4H), 7.17−7.16 (t, *J* = 7.5 Hz, 1H), 7.09−7.04 (m, 4H), 2.71 (q, *J* = 7.66 Hz, 2H), 1.26 (t, *J* = 7.75 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, CDC_{l3}) 192.9, 153.6, 150.8, 147.0, 145.5, 134.8, 134.2, 132.5, 131.6, 130.1, 128.6, 128.3, 128.1, 124.2, 124.2, 122.9, 119.1, 116.0, 29.2, 15.2; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}NO_2$ 354.1489, found 354.1481.

*(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(m-tolyl)methanone (**3e**).* The product was obtained as a yellow sticky solid (80%, 135 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.84 (s, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.40−7.34 (m, 5H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.13−7.07 (m, 4H) 2.42 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) *δ* 193.4, 153.6, 146.9, 145.4, 138.4, 136.5, 135.1, 134.5, 132.4, 131.7, 130.1, 128.6, 128.4, 127.2, 124.3, 124.2, 122.9, 119.1, 115.9, 21.4; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{18}NO_2$ 340.1332, found 340.1303.

https://doi.org/10.1021/acs.joc.2c01581
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(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(o-tolyl)methanone ***(3f)***. The product was obtained as a yellow solid (81%, 137 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 108−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 1H), 7.48 (s, 1H), 7.40−7.37 (m, 3H), 7.28−7.19 (m, 4H), 7.15 (t, J = 7.5 Hz, 1H), 7.07−7.00 (m, 4H) 2.61 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.5, 153.8, 146.2, 145.2, 139.1, 137.3, 135.8, 132.9, 131.9, 131.7, 131.6, 130.0, 128.6, 128.5, 125.4, 124.2, 124.1, 123.0, 119.1, 115.9, 21.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{18}NO_2$ 340.1332, found 340.1306.

(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(3,4,5-trimethoxyphenyl)-methanone ***(3g)***. The product was obtained as a brown solid (84%, 174 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 122−124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.38 (m, 3H), 7.31−7.28 (m, 4H), 7.18 (t, J = 7.5 Hz, 1H), 7.17 (s, 1H), 7.09 (d, J = 8.0 Hz, 2H), 3.94 (s, 3H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0, 153.1, 147.0, 145.2, 143.3, 135.1, 133.7, 132.1, 131.8, 131.4, 128.6, 128.4, 124.3, 124.3, 122.8, 119.0, 116.0, 107.5, 61.1, 56.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{22}NO_5$ 416.1492, found 416.1476.

(Z)-Benzo[d][1,3]dioxol-5-yl(2-(phenylimino)-2H-chromen-3-yl)-methanone ***(3h)***. The product was obtained as a brown solid (85%, 156 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.41−7.34 (m, 3H), 7.31−7.28 (m, 2H), 7.18−7.15 (m, 1H), 7.16−7.06 (m, 4H), 6.85 (d, J = 8.0 Hz, 1H), 6.04 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.3, 153.5, 152.4, 148.2, 147.0, 145.4, 134.6, 132.3, 131.6, 131.2, 128.6, 128.2, 127.0, 124.2, 124.2, 122.9, 119.0, 115.9, 109.1, 108.0, 102.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{16}NO_4$ 370.1074, found 370.1071.

(Z)-(4-Fluorophenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone ***(3i)***.[10] The product was obtained as a yellow solid (64%, 109 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 149−151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06−8.03 (m, 2H), 7.43−7.38 (m, 3H), 7.29 (t, J = 8.0 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.17−7.16 (m, 1H), 7.14 (s, 1H), 7.13−7.10 (m, 2H), 7.07 (d, J = 8.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.7, 166.1 (d, $^1J_{C-F}$ = 255.0 Hz), 153.7, 146.8, 145.2, 135.4, 133.0 (d, $^4J_{C-F}$ = 2.1 Hz), 132.4, (d, $^3J_{C-F}$ = 9.0 Hz), 132.0, 131.9, 128.6, 128.4, 124.4 (d, $^2J_{C-F}$ = 18.7 Hz), 122.9, 119.0, 116.0, 115.8, 115.6; HRMS (ESI-TOF) m/z [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 ***(3j)***.[10] The product was obtained as a yellow solid (69%, 123 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 168−170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.44−7.38 (m, 5H), 7.28-7.29 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.12−7.05 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.2, 153.7, 146.8, 145.1, 140.0, 135.8, 135.0, 132.0, 131.9, 131.1, 128.9, 128.6, 128.5, 124.5, 124.3, 122.9, 119.0, 116.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{15}NO_2Cl$ 360.0791, found 360.0785.

(Z)-(3-Bromophenyl)(2-(phenylimino)-2H-chromen-3-yl)-methanone ***(3k)***. The product was obtained as a sticky yellow solid (74%, 149 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.43−7.38 (m, 2H), 7.33 (t, J = 7.7 Hz, 1H), 7.29−7.24 (m, 2H), 7.17 (t, J = 7.50 Hz, 1H), 7.10−7.03 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0, 153.8, 146.7, 145.1, 138.5, 136.2, 136.19, 132.4, 132.1, 131.5, 130.1, 128.6, 128.6, 128.2, 124.4, 124.3, 122.8, 122.7, 118.9, 116.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{15}BrNO_2$ 404.0281, found 404.0264.

(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(4-(trifluoromethyl)-phenyl)methanone ***(3l)***.[10] The product was obtained as a yellow solid (70%, 137 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 112−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.51 (s, 1H), 7.45−7.40 (m, 2H), 7.29−7.25 (m, 2H), 7.19 (t, J = 7.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.5, 153.9, 146.6, 145.0, 139.7, 136.5, 134.7, 134.4, 132.3, 131.5, 129.8, 128.7, 125.6, 125.59 (q, $^2J_{CF3}$= 2.9 Hz), 124.6, 124.4, 123.7 (q, $^1J_{CF3}$ = 271.0 Hz), 122.9, 118.9, 117.4, 116.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{15}NO_2F_3$ 394.1055, found 394.1049.

(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(2-(trifluoromethyl)-phenyl)methanone ***(3m)***. The product was obtained as a yellow solid (70%, 137 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 110−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 2H), 7.75 (d, J = 6.5 Hz, 1H), 7.68−7.64 (m, 4H), 7.62−7.58 (m, 3H), 7.43 (d, J = 7.0 Hz, 1H), 7.36−7.34 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.7, 157.9, 155.6, 149.9, 138.7, 134.9, 131.8, 130.4, 130.3, 127.4, 127.1 126.6 (q, $^2J_{CF3}$ = 4.7 Hz), 125.1, 124.2, 123.7 (q, $^1J_{CF3}$ = 272.0 Hz), 118.1, 116.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{15}F_3NO_2$ 394.1049, found 394.1026.

(Z)-[1,1′-Biphenyl]-4-yl(2-(phenylimino)-2H-chromen-3-yl)-methanone ***(3n)***. The product was obtained as a yellow solid (78%, 152 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 195−197 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 7.5 Hz, 2H), 7.49- 7.39 (m, 6H), 7.29 (t, J = 8.0 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.12−7.07 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.8, 153.7, 146.9, 146.3, 145.4, 140.0, 135.2, 132.3, 131.8, 130.4, 129.2, 129.0, 128.6, 128.4, 128.4, 127.4, 127.2, 124.3, 124.2, 122.9, 119.1, 116.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{28}H_{20}NO_2$ 402.1489, found 402.1486.

(Z)-Naphthalen-2-yl(2-(phenylimino)-2H-chromen-3-yl)-methanone ***(3o)***. The product was obtained as a brown sticky solid (74%, 138 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.95−7.87 (m, 3H), 7.43 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.47 (s, 1H), 7.44−7.38 (m, 3H), 7.27−7.24 (m, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.07−7.04 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.2, 153.7, 147.0, 145.3, 135.9, 135.3, 133.9, 132.5, 132.3, 132.0, 131.8, 129.8, 128.7, 128.5, 128.4, 128.4, 127.9, 126.8, 125.0, 124.3, 124.2, 122.9, 119.1, 116.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{18}NO_2$ 376.1332, found 376.1330.

(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(thiophen-2-yl)-methanone ***(3p)***. The product was obtained as a brown sticky solid (78%, 129 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 3.5 Hz, 1H), 7.72 (d, J = 4.5 Hz, 1H), 7.43- 7.36 (m, 3H), 7.31 (t, J = 8.0 Hz, 2H), 7.18−7.13 (m, 4H), 7.11−7.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 153.6, 146.6, 145.3, 143.4, 135.1, 135.0, 134.9, 131.9, 131.7, 128.6, 128.4, 128.2, 124.3, 124.2, 122.9, 118.8, 115.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{14}NO_2S$ 332.0740, found 332.0735.

(Z)-(2-(Phenylimino)-2H-chromen-3-yl)(pyridin-3-yl)methanone ***(3q)***. The product was obtained as a brown sticky solid (74%, 120 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.77 (d, J = 8.0 Hz, 1H), 8.27 (dd, J^1 = 8.0 Hz, J^2 = 7.5 Hz, 1H), 7.55 (s, 1H), 7.45−7.41 (m, 3H), 7.29−7.27 (m, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.12−7.20 (m, 4H), ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.1, 153.9, 153.5, 151.0, 146.7, 144.9, 136.9, 136.5, 132.4, 132.3, 131.1, 128.8, 128.6, 124.5, 124.4, 123.5, 122.9, 118.9, 116.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{15}N_2O_2$, 327.1128 found 327.1116.

(Z)-(4-Chlorophenyl)(2-(p-tolylimino)-2H-chromen-3-yl)-methanone ***(3r)***. The product was obtained as a yellow solid (66%, 123 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 2H), 7.43−7.39 (m, 4H), 7.37 (d, J = 8.0 Hz, 1H), 7.17 (d, t = 7.5 Hz, 1H), 7.12−7.08 (m, 3H), 7.00 (d, J = 8.0 Hz, 2H), 2.84 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.2, 153.8, 146.4, 142.4, 139.9, 135.3, 135.1, 134.2, 132.1, 131.9, 131.0, 129.2, 128.8, 128.5, 124.2, 123.2, 119.1, 116.0, 21.1;

https://doi.org/10.1021/acs.joc.2c01581
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HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{16}ClNO_2$ 396.0762, found 396.0749.

*(Z)-(4-Fluorophenyl)(2-((4-methoxyphenyl)imino)-2H-chromen-3-yl)methanone (**3s**).* The product was obtained as a yellow solid (63%, 117 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 121−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−8.00 (m, 2H), 7.39 (t, J = 7.0 Hz, 1H), 7.35−7.34 (m, 2H), 7.16−7.09 (m, 6H), 6.81 (d, J = 4.0 Hz, 2H), 3.77 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 191.9, 167.0, 164.9, 156.9, 153.7, 145.9, 138.0, 134.5, 133.1, 133.1, 132.4, 132.3, 132.3, 131.7, 128.3, 125.1, 124.2, 119.1, 115.8, 115.7, 115.5, 113.8, 55.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{17}FNO_3$ 374.1187, found 374.1183.

*(Z)-Phenyl(2-(p-tolylimino)-2H-chromen-3-yl)methanone (**3t**).*[10] The product was obtained as a yellow solid (75%, 127 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 129−131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.41−7.35 (m, 3H), 7.16 (t, J = 7.5 Hz, 1H), 7.12−7.07 (m, 3H), 7.00 (d, J = 8.0 Hz, 2H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.4, 153.8, 146.5, 142.5, 136.6, 134.8, 134.0, 133.5, 132.5, 131.7, 129.7, 129.2, 128.5, 128.4, 124.1, 123.2, 119.2, 115.9, 21.1. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{18}NO_2$ 340.1338, found 340.1345.

*(Z)-(2-((2-Chlorophenyl)imino)-2H-chromen-3-yl)(phenyl)-methanone (**3u**).* The product was obtained as a yellow solid (73%, 131 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 100−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.2 Hz, 5H), 7.50−7.39 (m, 5H), 7.22−7.18 (m, 2H), 7.13 (d, J = 8.5 Hz, 1H), 7.08−7.03 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.0, 153.5, 147.7, 146.7, 136.4, 135.8, 134.0, 133.7, 132.0, 131.8, 129.7, 129.6, 128.6, 128.5, 124.5, 124.2, 122.9, 121.2, 118.9, 116.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{15}ClNO_2$, 360.0786, found 360.0762.

*(Z)-(6-Methoxy-2-(p-tolylimino)-2H-chromen-3-yl)(phenyl)-methanone (**3v**).* The product was obtained as a brown solid (72%, 132 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 100−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.2 Hz, 2H), 7.33 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.09−7.06 (m, 3H), 6.99 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 7.5 Hz, 1H), 3.87 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 193.6, 147.1, 145.7, 143.4, 141.9, 136.7, 134.6, 134.5, 133.4, 132.9, 129.6, 129.0, 128.4, 124.6, 123.9, 119.9, 119.8, 114.5, 56.6, 21.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{20}NO_3$, 370.1438, found 370.1429.

*(Z)-(6-Bromo-2-(phenylimino)-2H-chromen-3-yl)(4-methoxyphenyl)methanone (**3w**).* The product was obtained as a yellow solid (62%, 134 mg, purified by silica gel column chromatography eluting with 10% ethyl acetate in 90% hexane): mp 178−180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 9.0 Hz, 2H), 7.47−7.46 (m, 2H), 7.30−7.27 (m, 2H), 7.25 (s, 1H), 7.15 (t, J = 7.7 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.99−6.94 (m, 3H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): 191.2, 164.3, 152.5, 146.3, 145.1, 134.1, 132.9, 132.3, 130.5, 128.6, 124.5, 122.9, 120.9, 117.6, 116.5, 115.2, 113.9, 55.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{17}BrNO_3$ 434.0386, found 434.0348.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01581.

Experimental procedures and spectroscopic characterization data (PDF)

FAIR data, including the primary NMR FID files, for compounds **3** (ZIP)

Accession Codes

CCDC 2182043 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from the Science and Engineering Research Board (CRG/2019/000058) and JC Bose National Fellowship (JCB/2020/000023), New Delhi. The authors (PP and DY) are thankful to UGC, New Delhi for fellowship. We also acknowledge the support of IoE Incentive Grant (Scheme No. 6031) and DST-FIST for basic and high-end analytical facilities to the department.

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(14) CCDC 2182043 contains the supplementary crystallographic data for the compound **3f** reported in this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

https://doi.org/10.1021/acs.joc.2c01581
J. Org. Chem. 2022, 87, 12342−12351