ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

D-Glucosamine as the Green Ligand for Cu(I)-Catalyzed Regio- and Stereoselective Domino Synthesis of (*Z*)-3-Methyleneisoindoline-1-ones and (*E*)-*N*-Aryl-4*H*-thiochromen-4-imines

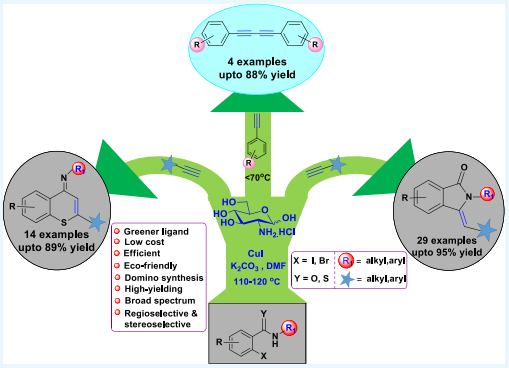
Sumit K. Singh, Mangal S. Yadav, Anoop S. Singh, Anand K. Agrahari, Nidhi Mishra, Sunil Kumar, and Vinod K. Tiwari*

Cite This: *ACS Omega* 2021, 6, 21125−21138

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: D-Glucosamine, a natural, inexpensive, and conveniently accessible sugar, has been explored as an efficient ligand for the Cu(I)-catalyzed regio- and stereoselective synthesis of an array of (*Z*)-3-methyleneisoindoline-1-ones and (*E*)-*N*-aryl-4*H*-thiochromen-4-imines in good-to-excellent yield in a tandem fashion *via* the reaction of 2-halobenzamide and 2-halobenzothioamide with terminal alkynes, respectively. The water solubility and biocompatible nature of the ligand offer easy separation of the catalytic system toward the aqueous phase as well as change in the reaction path in terms of the product also demonstrated the variation of the reaction temperature. The domino reaction proceeds by the Sonogashira and Ullmann type cross-coupling reaction, followed by Cu(I)-promoted additive cyclization of heteroatom to the triple bond. In addition, D-glucosamine causes successful Glaser−Hay coupling of terminal alkynes under Cu catalysis to produce a high yield of respective 1,3-diynes.

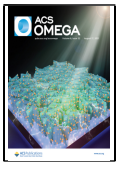


INTRODUCTION

The heterocyclic motif of substituted 3-methyleneisoindoline-1-ones and its analogues constitute an important class of biologically relevant natural products as well as designed medicinal agents.[1] A number of structures were explored as promising drug conjugates, and they show numerous biological activities such as antivasoconstriction,[2] antianxiety,[3] sedative,[4] antileukemic,[5] antiviral,[6] antipsychotic, and anti-inflammatory.[7] Representative examples of biologically relevant natural products and new chemical entities (NCEs) derived from the 3-methyleneisoindolin-1-one core are AKS 186 (**I**),[8] fumaridine (**II**),[9] narceine imide (**III**),[10] fumaramidine (**IV**),[11] fumaramine (**V**),[12] (*R*)-PD 172939 (dopamine D4 antagonist) (**VI**),[13] lennoxamine (**VII**),[14] aristoyagonine (**VIII**),[15] allosteric agent (**IX**),[16] and (*S*)-pazinaclone (**X**)[17] (Figure 1). In addition to methyleneisoindoline-1-ones, derivatives of thiochromene-4-imines also show a myriad of potential biological activities, such as antiproliferative,[18] antiemetic,[19] antioxidant,[20] antibacterial,[21] and anti-HIV,[22] which intensify the importance of new suitable approaches for the synthesis of these derivatives. One of the most efficient and convenient methods for the synthesis of methyleneisoindoline-1-ones and thiochromene-4-imines analogues include the ligand-promoted transition metal-catalyzed carbon−carbon or carbon-heteroatom coupling reaction, followed by additive cyclization on the triple bond.[23] Several conventional and new ligand stabilized Cu(I) and Pd(II) are the more frequently used transition metals for the synthesis of these derivatives. Moreover, most of the catalytic systems applied for these reactions require high loading of a ligand as well as a Cu source.[24] For a notable example, a library of 3-methyleneisoindolin-1-one analogues were developed in good yields by reacting 2-bromobenzamides with terminal alkynes *via* CuI-mediated tandem reaction using 30 mol % of L-proline.[24b] The classical method for the synthesis of 3-methyleneisoindoline-1-ones involved Wittig reaction on phthalimide, where this approach suffers from poor regioselectivity with unsymmetrical substrates.[25]

In addition to the existing ligands including L-proline, carbohydrate-based ligands have received considerable attention in recent years for the synthesis of a number of biologically relevant molecules of chemotherapeutic potential.[26] The most apparent reasons for the selection of carbohydrates or their derivatives include their biocompatible nature, easy accessibility, and low cost. In addition, spatial arrangement of multiple free hydroxy groups attached to the rigid pyranose structure of the carbohydrate moiety and straightforward transformation of these hydroxy groups to a

Received: June 8, 2021
Accepted: July 14, 2021
Published: August 4, 2021



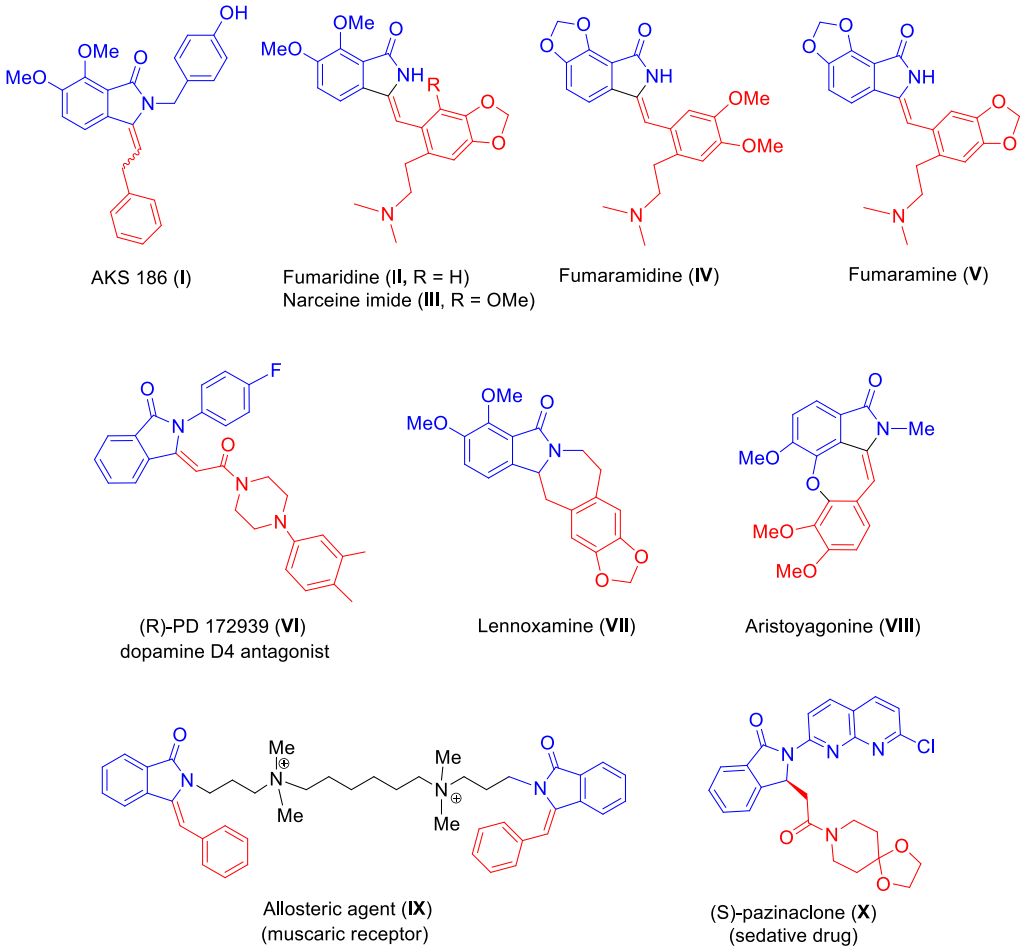


Figure 1. Structures of some biologically relevant natural products and NCEs derived from the 3-methyleneisoindolin-1-one core.

variety of desired functionalities offer wide prospects to modify them to appropriate ligands useful in organic synthesis.[26] Sekar and co-workers, in 2011, reported the first Cu-catalyzed amination reaction with the D-glucosamine ligand, but the method was limited to amination reaction.[27a] It is noteworthy to mention that D-glucosamine and its derivatives have been explored in past as ligands in catalytic systems in a number of important reactions.[27] Notably, Tripathi and co-workers, in 2008, explored the same D-glucosamine as an appropriate organocatalyst in the direct aldol reaction of ketones with aromatic aldehyde in water.[27b] The most important necessity of synthetic organic chemistry is to change the conventional catalytic system *via* the eco-friendly catalytic system. Thus, in this report, we have explored the greener aspect of D-glucosamine for Cu(I)-catalyzed synthesis of (*Z*)-3-methyleneisoindoline-1-one, (*E*)-*N*-aryl-4*H*-thiochromen-4-imines, and dialkyne analogues with low catalytic loading and easily separable and a single catalytic system applicable for Sonogashira and Ullmann type cross-coupling reaction. The devised protocol also offers regioselective additive-cyclization with a good-to-excellent yield of the biologically relevant domino products.

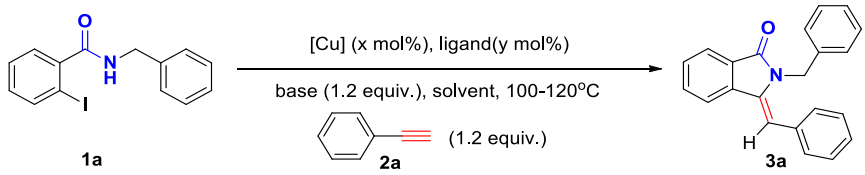
RESULTS AND DISCUSSION

At first, for the optimization of reaction conditions and identification of catalytic performance of the ligands, an appropriate source of Cu, suitable base, and solvent, a model reaction was set for the Sonogashira coupling, followed by additive cyclization of *N*-benzyl-2-iodobenzamide (**1a**) with phenylacetylene (**2a**) to obtain (*Z*)-3-methyleneisoindoline-1-ones (**3a**). The results are summarized in Table 1.

For the catalytic screening of natural and conventional ligands, 1.0 equiv of *N*-benzyl-2-iodobenzamide (**1a**) and 1.2 equiv. of phenylacetylene (**2a**) were heated with 10 mol % CuI as the Cu source, 10 mol % ligands, and 1.2 equiv of the base in 2 mL of anhydrous DMF as solvent at 120 °C in a sealed tube for 12 h. Initially, we have used natural ligands with free hydroxyl groups such as D-mannose (**L1**), D-glucose (**L2**), D-xylose (**L3**), and α-D-methylglucopyranoside (**L4**) with a yield of product (**2a**) in the range of 62−65%. Catalysis with *N*-acetyl-D-glucosamine (**L5**) and D-glucosamine (**L6**) resulted in a good yield of the product in comparison to the free hydroxyl group based natural and free hydroxyl and amino group based conventional ligands such as propane-1,2-diamine (**L7**) and ethylene glycol (**L8**). The best result in terms of yields of product **3a** was obtained with ligand **L6** (Table 1, entry 6). Only a 35% yield of product **3a** was obtained when no ligand was used (Table 1, entry 10). Further investigation studies were extended for Cu sources other than CuI; the screened results proved that other Cu sources such as CuCl, CuOAc, $Cu(OAc)_2·H_2O$, $CuSO_4$, and Cu_2O remain less reactive in terms of the yield of the product (Table 1, entry 26−30), whereas no product was obtained in the absence of the Cu source (Table 1, entry 15). Next, the reaction was investigated in the presence of organic bases (Et_3N and DBU) over inorganic bases (K_2CO_3, K_3PO_4, and Cs_2CO_3); the inorganic

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

Table 1. Screening of Ligands L1−L8 and Optimization of the Reaction Conditions[a]



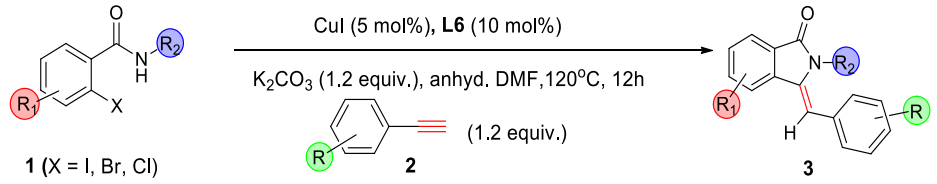
entry	ligand	[Cu]	base	solvent	yield[b] (in %)
1	**L1**	CuI	K_2CO_3	DMF	65
2	**L2**	CuI	K_2CO_3	DMF	68
3	**L3**	CuI	K_2CO_3	DMF	62
4	**L4**	CuI	K_2CO_3	DMF	65
5	**L5**	CuI	K_2CO_3	DMF	82
6	**L6**	**CuI**	**K_2CO_3**	**DMF**	**88**
8	**L7**	CuI	K_2CO_3	DMF	55
9	**L8**	CuI	K_2CO_3	DMF	52
10		CuI	K_2CO_3	DMF	35
11[c]	**L6**	CuI	K_2CO_3	DMF	86
12[d]	**L6**	CuI	K_2CO_3	DMF	84
13[e]	...	CuI	K_2CO_3	DMF	<17
14[f]	**L6**	**CuI**	**K_2CO_3**	**DMF**	**88**
15	**L6**		K_2CO_3	DMF	NR
16	**L6**	CuI	K_3PO_4	DMF	80
17	**L6**	CuI	Cs_2CO_3	DMF	78
18	**L6**	CuI	Et_3N	DMF	45
19	**L6**	CuI	DBU	DMF	55
20	**L6**	CuI	...	DMF	NR
21	**L6**	CuI	K_2CO_3	toluene	15
22	**L6**	CuI	K_2CO_3	DCM	30
23	**L6**	CuI	K_2CO_3	DMSO	86
24	**L6**	CuI	K_2CO_3	THF	20
25	**L6**	CuI	K_2CO_3	EtOH	82
26	**L6**	CuCl	K_2CO_3	DMF	75
27	**L6**	CuOAc	K_2CO_3	DMF	70
28	**L6**	$Cu(OAc)_2·H_2O$	K_2CO_3	DMF	66
29	**L6**	$CuSO_4$	K_2CO_3	DMF	50
30	**L6**	Cu_2O	K_2CO_3	DMF	65

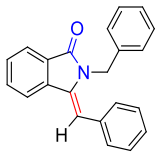
[a]Molar ratios: *N*-benzyl-2-iodobenzamide (1.0 equiv), phenylacetylene (1.2 equiv), ligands (10 mol %), Cu source (10 mol %), base (1.2 equiv), solvent (2 mL), temperature 120 °C, reaction time 12 h. [b]Yields reported after purification by column chromatography (SiO_2). [c]**L6** (20 mol %). [d]*N*-Benzyl-2-bromobenzamide (1.0 equiv) in place of *N*-benzyl-2-iodobenzamide, temperature 140 °C. [e]*N*-Benzyl-2-bromobenzamide (1.0 equiv). [f]**L6** (10 mol %), CuI (5 mol %). (**L1**) D-mannose, (**L2**) D-glucose, (**L3**) D-xylose, (**L4**) α-D-methylglucopyranoside, (**L5**) *N*-acetyl-D-glucosamine, (**L6**) D-glucosamine, (**L7**) propane-1,2-diamine, and (**L8**) ethylene glycol.

bases gave an excellent yield over organic bases (Table 1, entry 14[f], 16−19), whereas no product was obtained in the absence of the base (Table 1, entry 20). The catalytic amount of the ligand becomes more important with change in halo substituents of the substrate from a good leaving group to a poor leaving group; less than 17% yield of the desired product was obtained from *N*-benzyl-2-bromobenzamide in the absence of the ligand (Table 1, entry 13[e]), whereas 84% yield of the product resulted in the presence of the ligand (Table 1, entry 12[d]). The formation of product **3a** was confirmed on the basis of ^1H and ^{13}C NMR and mass spectrum analysis, which was found in agreement with the literature.[28] The optimal Cu salt loading was found to be 5 mol %; further increasing the Cu salt loading gave a similar yield of product. The optimized reaction conditions for the synthesis of (*Z*)-2-benzyl-3-benzylideneisoindolin-1-one (**3a**) from *N*-benzyl-2-iodobenzamide (**1a**) and phenylacetylene (**2a**) involving 5 mol % CuI, 10 mol % ligand **L6**, 1.2 equiv of K_2CO_3 in anhydrous DMF, and 100−120 °C temperature were investigated with different sets of 2-halobenzamides (**1**) that differ in substitution in the aromatic ring as well as at N-atom of the amide linkage and a variety of aliphatic and aromatic terminal alkynes (Scheme 1). A comparatively slower reaction and slightly lower yield were obtained in the case of *N*-benzyl-2-chloro-benzamide than that of the respective bromo and iodo analogue **3a** (Scheme 1). No remarkable variation in yields was observed with different substitutions at different positions of the phenyl ring attached to terminal alkyne; however, reaction takes place in a smooth manner and slightly higher yield with the phenyl ring substituted with electron-withdrawing groups (compounds **3f**, **3g**, **3l**, **3m**, **3t**, and **3y**, Scheme 1). An exceptional decrease in the yield of the product was observed with the aliphatic group substituted terminal alkyne (**3h**, Scheme 1), which may arise due to the electronic factor of the aryl substituent on the additive cyclization step. The substituent attached to N-atom of the 2-halo-amide substrate also affects the yield of the reaction product. A slightly lower yield of the product was observed

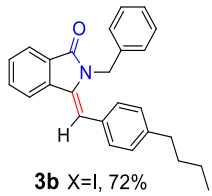
https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

Scheme 1. Synthesis of 3-Methyleneisoindoline-1-ones (3a−3ac) *via* Optimized Reaction Conditions[a]

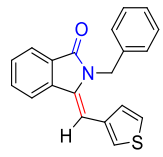




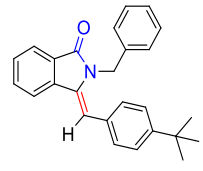
3a X=I, 88%
X=Br, 86%,16h
X=Cl, 55%, 24h



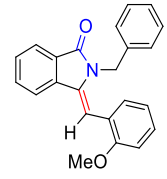
3b X=I, 72%
X=Br, 72%,14h



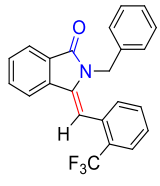
3c X=I, 82%



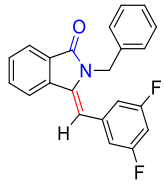
3d X=I, 75%
X=Br, 74%,16h



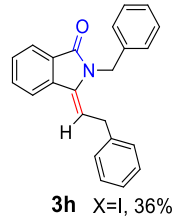
3e X=I, 60%



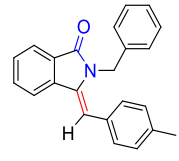
3f X=I, 74%



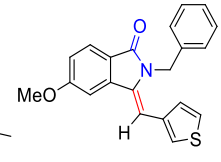
3g X=I, 90%



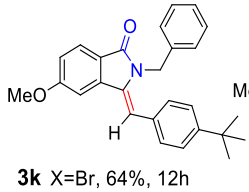
3h X=I, 36%



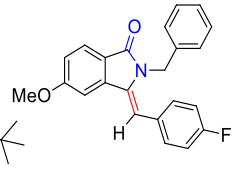
3i X=I, 62%



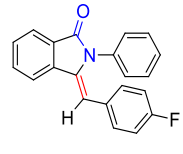
3j X=Br, 77%, 12h



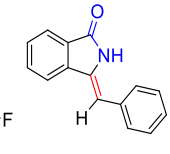
3k X=Br, 64%, 12h



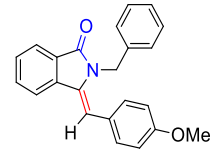
3l X=Br, 75%, 14h



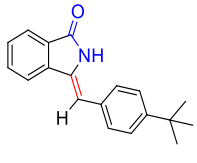
3m X=I, 87%



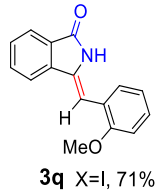
3n X=I, 82%



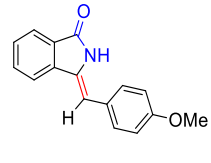
3o X=I, 78%



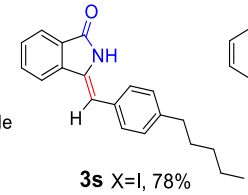
3p X=I, 83%



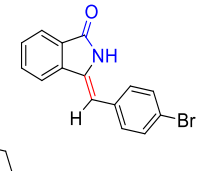
3q X=I, 71%



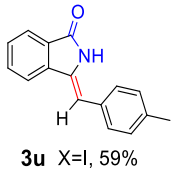
3r X=I, 52%



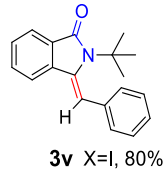
3s X=I, 78%



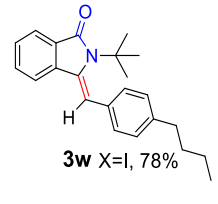
3t X=I, 84%



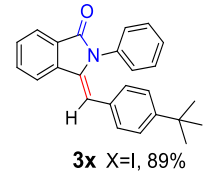
3u X=I, 59%



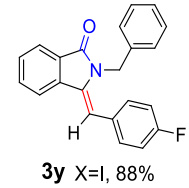
3v X=I, 80%



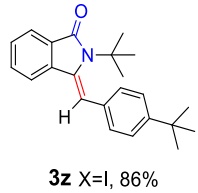
3w X=I, 78%



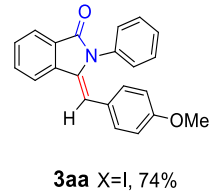
3x X=I, 89%



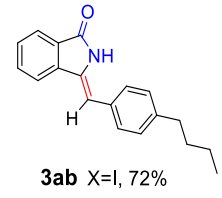
3y X=I, 88%



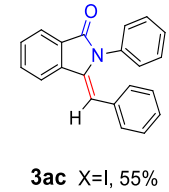
3z X=I, 86%



3aa X=I, 74%



3ab X=I, 72%



3ac X=I, 55%

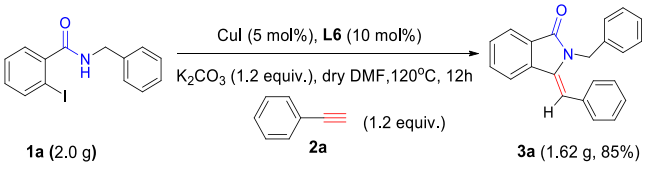
[a]Yields in % reported after purification by column chromatography (SiO_2).

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

with phenyl substituted N-atom in comparison to unprotected or alkyl group substituted N-atom (compound **3ac**, **3n**, and **3v**, Scheme 1).

The efficacy of reaction was also tested with 2-bromobenzamide instead of 2-iodobenzamide, which gave a comparatively similar yield but required more reaction time (Scheme 1). In all reaction conditions, predominantly a single stereoisomer (*Z*-isomer) of the product was observed. The formation of *Z*-isomer was confirmed by comparing the spectral data of the synthesized compound with those reported in the literature.[29] For the quantitative estimation of the reactions catalyzed with the Cu(I)/**L6** catalytic system, we carried out reactions on the gram scale and found a good yield of compound **3a** (Scheme 2).

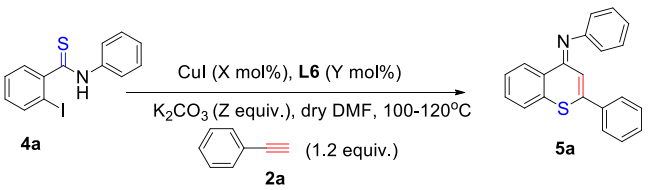
Scheme 2. Gram Scale Reactions for the Synthesis of (*Z*)-2-Benzyl-3-Benzylideneisoindolin-1-one 3a Using Ligand L6[a]



[a]Yields in % reported after purification by column chromatography (SiO_2).

After the success of the D-glucosamine ligand for the Sonogashira coupling followed by cyclative additive amination, we moved forward with the same catalytic system for the practical synthesis of (*E*)-*N*-aryl-4*H*-thiochromen-4-imines (**5**) from cascade reaction between 2-iodobenzothioamide (**4**) and terminal alkynes (**2**) under optimized conditions. *N*-phenyl-2-iodobenzothioamide (**4a**) and phenylacetylene (**2a**) were selected as the model substrates and treated with CuI, D-glucosamine, and K_2CO_3 as the base in anhydrous DMF as solvent at 100−120 °C. Optimization of reaction conditions with respect to the molar ratios of **L6**, CuI, and K_2CO_3, temperature, and reaction time has been summarized in Table 2. The optimized reaction condition for the synthesis of (E)-*N*-(2-phenyl-4*H*-thiochromen-4-ylidene)aniline (**5a**) from *N*-phenyl-2-iodobenzothioamide (**4a**) and phenylacetylene (**2a**) was established, where 5 mol % CuI and 10 mol % **L6** in the presence of 1.2 equiv of K_2CO_3 in anhydrous DMF as solvent at 120 °C for 12 h reaction time resulted in a good yield of product **5a** (Table 2, entry 4).

Table 2. Reaction Optimization for the Application of L6 in Tandem Synthesis of (E)-*N*-Aryl-4*H*-thiochromen-4-imine (5a)



entry	CuI (mol %)	**L6** (mol %)	K_2CO_3 (equiv)	temp	time (h)	yield[a] (%)
1	10	20	1.2	120	12	85
2	10	10	1.2	120	12	86
3	10	5	1.2	120	12	72
4	**5**	**10**	**1.2**	**120**	**12**	**86**
5	5	10	1.2	120	18	86
6	5	10	1.5	120	12	85
7	5	10	1.2	140	12	85

[a]Yields in % reported after purification by column chromatography (SiO_2).

The optimized reaction condition was investigated with different sets of 2-halobenzothioamides (**4**) and terminal alkynes (**2**). No remarkable variation in yields was observed with different substitutions at different positions of the phenyl ring attached to terminal alkynes (Scheme 3).

In addition to the synthesis of (*Z*)-3-methyleneisoindoline-1-ones and (*E*)-*N*-aryl-4*H*-thiochromen-4-imines, the glucosamine ligand **L6** is also applied for the Cu(I)-catalyzed Glaser−Hay coupling of terminal alkyne (**2**) with optimized reaction conditions and molar ratios that resulted in the formation of 1,4-bis(4-(*tert*-butyl)phenyl)buta-1,3-diyne (**6a**) and other derivatives (**6b**−**d**) in 56−88% yields (Scheme 4).

A plausible mechanism for the synthesis of (*Z*)-3-methyleneisoindoline-1-ones (**3**) and (*E*)-*N*-aryl-4*H*-thiochromen-4-imines (**5**) is depicted in Schemes 5 and 6. According to postulations,[30] ligand **L6** coordinates with Cu(I) as a bidentate ligand. The 2-halobenzamide substrate (**1**) undergoes oxidative addition on the ligand coordinated Cu(I) system (**A**) to form respective coordinated intermediate **B**, which on reaction with alkynyl copper results in the formation of intermediate **C**. Intermediate **C** on reductive elimination produces compound **D** and the ligand coordinated Cu(I) (**A**) system. In the final step, compound **D** furnishes (*Z*)-3-methyleneisoindoline-1-ones **3** in the presence of CuI and K_2CO_3 *via* cyclative additive amination (Scheme 5).

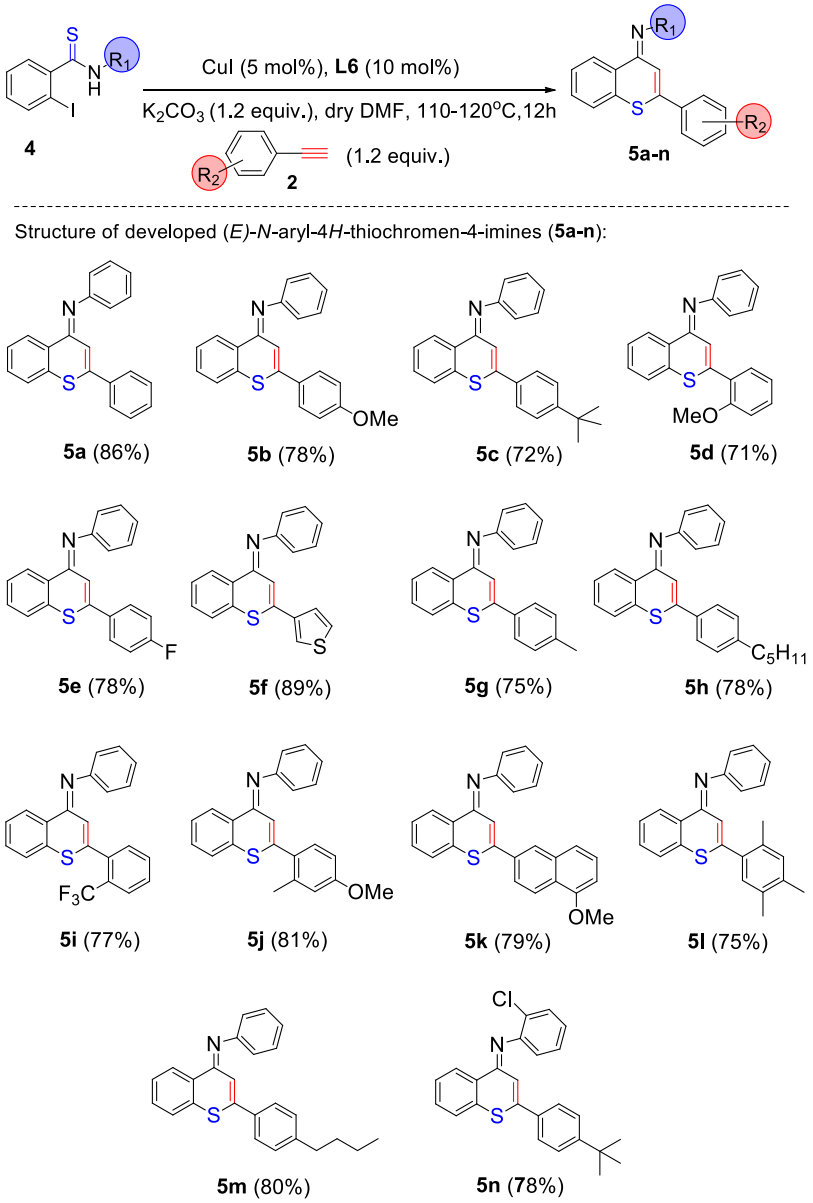
On the other hand, in the synthetic route of (*E*)-*N*-aryl-4*H*-thiochromen-4-imines (**5**), copper(I) complex **F** could be formed by the coordination of ligand **L6** with CuI, which on oxidative addition of the C−I bond of substrate **4** leads to the formation of copper complex **G**.[31] Base-promoted deprotonation of complex **G** resulted in the sulfur-centered anion **H**, which on releasing the halide ion produced intermediate **I**. Reductive elimination of intermediate **I** furnishes the regenerated Cu(I) complex and 4*H*-benzothietane-2-imine **J** (*via* C−S bond formation),[31] which gets converted into final product **5** *via* a nucleophilic attack of the alkynyl group, followed by cyclative rearrangement in the presence of K_2CO_3 and CuI (Scheme 6).

CONCLUSIONS

In conclusion, we have developed the D-glucosamine/CuI system as a simple, efficient, inexpensive, and biocompatible catalytic system for easy access to (*Z*)-3-methyleneisoindoline-1-ones as well as (*E*)-*N*-aryl-4*H*-thiochromen-4-imines in tandem one-pot fashion with excellent regio- and stereoselectivity. It is a single catalytic system that is applicable for Sonogashira, Ullmann, Glaser−Hay coupling reactions and finally in the domino synthesis of several novel heterocyclic motifs of biological relevance. Utilizing the D-glucosamine/CuI-mediated tandem route, we developed 29 different (*Z*)-3-methyleneisoindoline-1-ones (where 13 are new) and 14 different (*E*)-*N*-aryl-4*H*-thiochromen-4-imines (where 12 are new). In short, a total of 47 analogues of biologically relevant heterocycles and diynes were developed herein with great ease and high-to-excellent yields. D-Glucosamine exhibited several notable advantages, such as broad application scope, mild reaction conditions, simple operation, eco-friendliness, and

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

Scheme 3. Synthesis of (*E*)-*N*-Aryl-4*H*-thiochromen-4-imines (5a−n) *via* Optimized Reaction Conditions[a]



[a]Yields (in %) reported after purification by column chromatography (SiO_2).

produced a good-to-excellent yield of the product with comparatively low catalyst loading.

EXPERIMENTAL SECTION

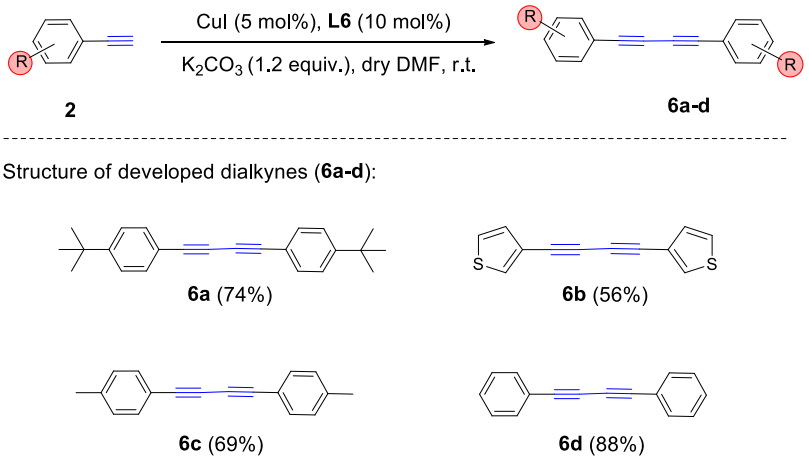
General. All the reactions were performed under an argon atmosphere using analytical grade reagents and dry solvents. Glassware was dried in an oven at 100 °C for 1 h and cooled in a desiccator before use. Next, 60 F254 silica gel precoated aluminum plates were used for TLC, and the spots were located under a UV lamp (λ_{max} = 254 nm). ^{1}H and ^{13}C NMR were recorded on a JEOL NMR spectrometer at 500 and 125 MHz, respectively. The chemical shifts given in parts per million (ppm) are relative to that of tetramethylsilane as an internal standard; the *J* values are given in hertz. Mass spectra were recorded by electron spray ionization mass spectrometry. The melting points were determined using an open capillary on a melting point apparatus.

General Procedure for the Syntheses of (*Z*)-3-Methyleneisoindoline-1-ones. 2-Iodobenzamide **1a** (200 mg, 0.59 mmol) was put in anhydrous DMF (4 mL), and ligand **L6** (10 mol %, 12 mg, 0.059 mmol), CuI (5 mol %, 7 mg, 0.03 mmol), terminal alkyne (**2a**, 83 mg, 0.70 mmol, 88 μL), and K_2CO_3 (1.2 equiv, 98 mg, 0.71 mmol) were added to it. The mixture was heated at 120 °C in a sealed tube under an argon atmosphere for 12 h. Completion of the reaction was confirmed by TLC, and the reaction mass was cooled to room temperature, followed by the evaporation of DMF under reduced pressure. The crude residue was purified by column chromatography (230−400 mesh silica gel) to provide product **3a** using a mixture of ethyl acetate and *n*-hexane (1:9) as the eluent.

*(Z)-2-Benzyl-3-benzylideneisoindolin-1-one (**3a**).*[28c] Light yellow solid, yield 88%; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 110−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H),

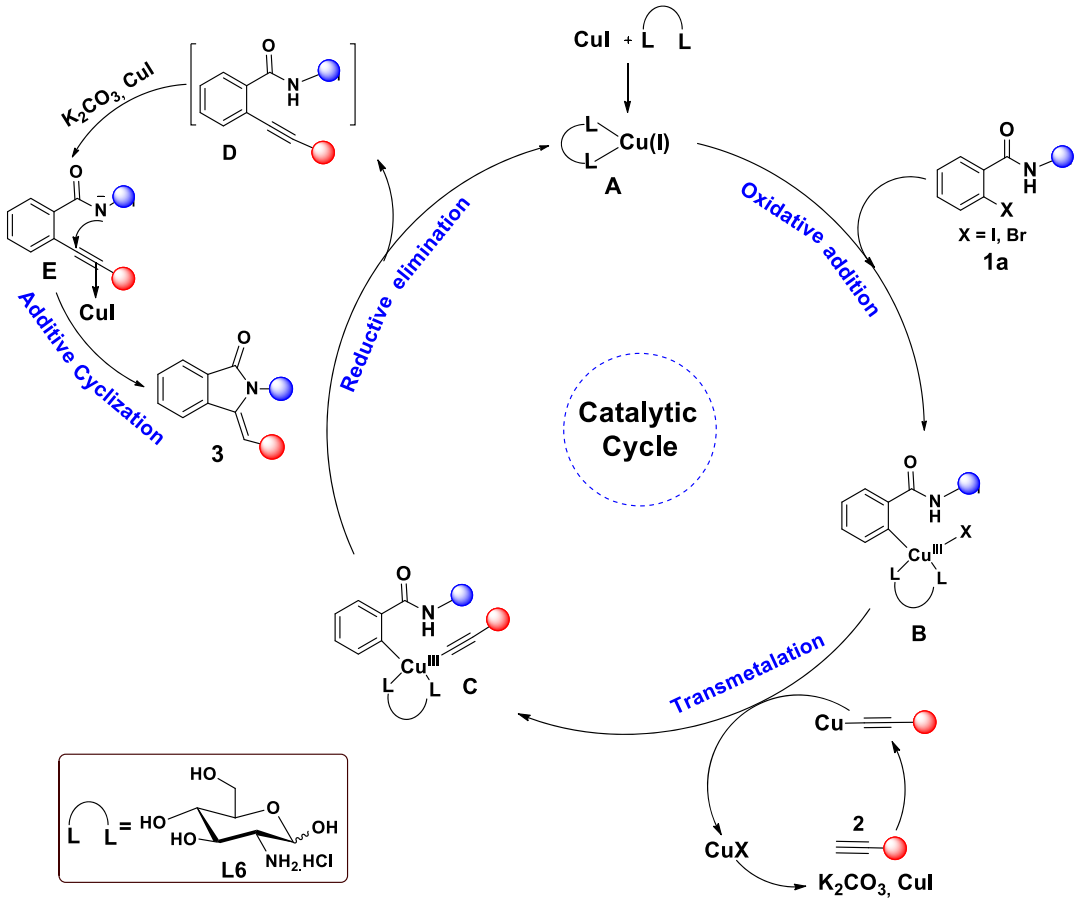
https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

Scheme 4. Synthesis of Dialkynes (6a–d) *via* Optimized Reaction Conditions[a]



[a]Yields (in %) reported after purification by column chromatography (SiO_2).

Scheme 5. Plausible Mechanism for Cu-L6 Catalyzed Synthesis of (Z)-3-Methyleneisoindoline-1-ones (3)



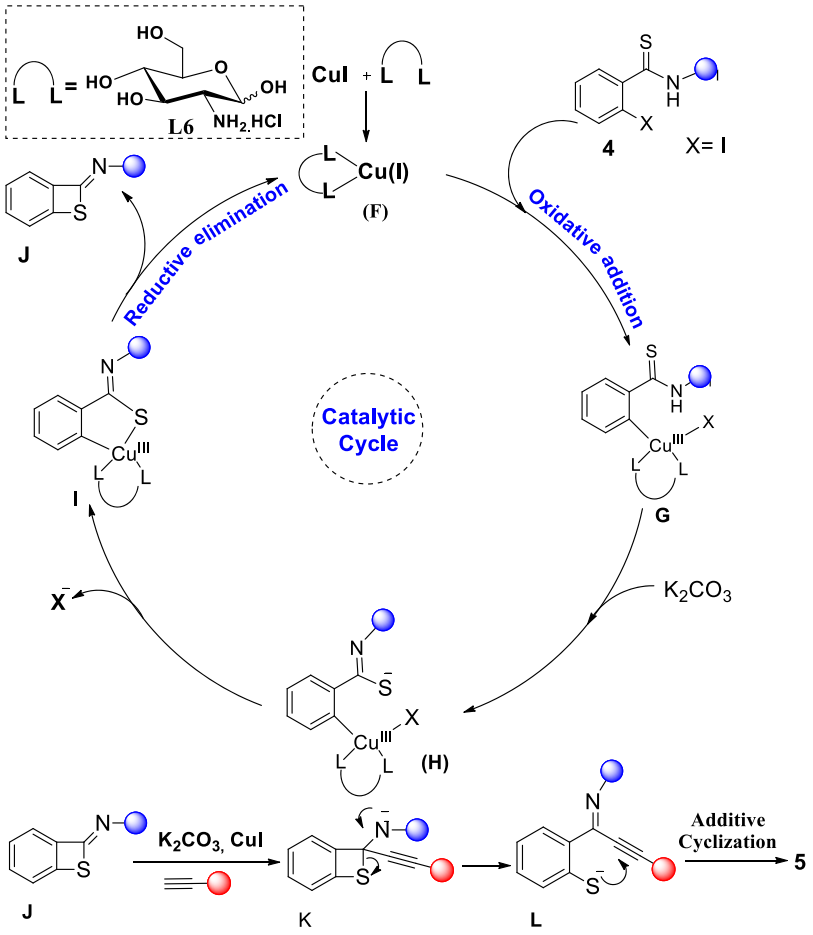
7.52 (t, J = 7.5 Hz, 1H), 7.27–7.22 (m, 3H), 7.09–7.02 (m, 5H), 6.71 (s, 1H), 6.53 (d, J = 6.5 Hz, 2H), 4.93 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 138.4, 136.7, 134.5, 134.2, 132.0, 129.5, 128.9, 128.0, 127.9, 127.8, 127.3, 126.6, 126.2, 123.4, 119.3, 107.4, and 44.8 ppm.

*(Z)-2-Benzyl-3-(4-butylbenzylidene)isoindolin-1-one (**3b**).* Light yellow gel, 156 mg, 72% yield; R_f = 0.7 (15% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.62–7.59 (m, 1H), 7.53–7.50 (m, 1H), 7.09–7.03 (m, 5H), 6.99 (d, J = 7.5 Hz, 2H), 6.71 (s, 1H), 6.55 (d, J = 6.5 Hz, 2H), 4.97 (s, 2H), 2.64 (t, J = 7.5 Hz, 2H), 1.68–1.62 (m, 2H), 1.45–1.38 (m, 2H), 1.00–0.97 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 142.2, 138.4, 136.8, 133.9, 131.9, 131.6, 129.4, 128.8, 128.0, 127.9, 127.8, 126.5, 126.3, 123.3, 119.3, 107.7, 44.7, 35.3, 33.6, 22.2, and 13.9 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{26}H_{26}NO^+$, 368.2009; found, 368.2010.

*(Z)-2-Benzyl-3-(thiophen-3-ylmethylene)isoindolin-1-one (**3c**).* Light yellow solid, 154 mg, 82% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 109–111 °C; ^{1}HNMR (500 MHz,

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125–21138

Scheme 6. Plausible Mechanism for Cu-L6 Catalyzed Synthesis of (*E*)-*N*-Aryl-4*H*-thiochromen-4-imines (5)



$CDCl_3$): δ 7.93 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.62−7.59 (m, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.23−7.22 (m, 1H), 7.12 (q, J = 2.2 Hz, 3H), 6.94 (t, J = 2.0 Hz, 1H), 6.80 (d, J = 4.5 Hz, 1H), 6.69−6.67 (m, 2H), 6.56 (s, 1H), 5.01 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 138.2, 136.9, 134.9, 134.5, 132.0, 129.2, 129.0, 128.0, 127.9, 126.7, 126.1, 125.1, 124.2, 123.4, 119.3, 102.0, and 44.6 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{16}NOS^+$, 318.0947; found, 318.0954.

(Z)-2-Benzyl-3-(4-(tert-butyl)benzylidene)isoindolin-1-one ***(3d)***. Light yellow solid, 162 mg, 75% yield; R_f = 0.7 (15% ethyl acetate/*n*-hexane), mp 104−106 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.56−7.53 (m, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 2H), 7.02 (d, J = 6.5 Hz, 1H), 6.98 (t, J = 6.5 Hz, 2H), 6.93 (d, J = 7.5 Hz, 2H), 6.66 (s, 1H), 6.45 (d, J = 7.5 Hz, 2H), 4.91 (s, 2H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 150.4, 138.4, 136.8, 134.1, 132.0, 131.4, 129.3, 128.8, 128.0, 127.8, 126.5, 126.2, 124.6, 123.4, 119.3, 107.6, 44.8, 34.5, and 31.2 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{26}H_{26}NO^+$, 368.2009; found, 368.1996.

(Z)-2-Benzyl-3-(2-methoxybenzylidene)isoindolin-1-one ***(3e)***. Yellow solid, 121 mg, 60% yield; R_f = 0.4 (15% ethyl acetate/*n*-hexane), mp 139−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.29−7.26 (m, 1H), 7.10−7.01 (m, 4H), 6.91−6.89 (m, 1H), 6.72 (d, J = 8.5 Hz, 1H), 6.62 (s, 1H), 6.53 (d, J = 7.5 Hz, 2H), 4.94 (s, 2H), 3.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 157.6, 138.4, 136.8, 134.4, 131.9, 131.4, 129.2, 128.8, 128.0, 127.8, 126.4, 126.3, 123.4, 123.3, 119.7, 119.7, 110.2, 104.3, 55.1, and 44.7 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{20}NO_2^+$, 342.1489; found, 342.1469.

(Z)-2-Benzyl-3-(2-(trifluoromethyl)benzylidene)isoindolin-1-one ***(3f)***. White solid, 165 mg, 74% yield; R_f = 0.4 (15% ethyl acetate/*n*-hexane), mp 109−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.56−7.53 (m, 1H), 7.50−7.47 (m, 2H), 7.45 (t, J = 7.3 Hz, 1H), 7.35−7.31 (m, 4H), 7.29−7.26 (m, 2H), 6.80 (d, J = 7.5 Hz, 1H), 6.50 (s, 1H), 5.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 136.9, 136.4, 134.8, 133.8, 132.0, 131.7 (d, $^3J_{C-F}$ = 19.0 Hz), 130.3, 129.5, 129.5, 129.3, 128.7, 128.1, 128.0, 127.4, 127.0, 126.3 (q, $^1J_{C-F}$ = 19.0 Hz), 125.9, 124.8, 123.5, 123.1, 122.6, 107.4, and 43.3 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{17}F_3NO^+$, 380.1257; found, 380.1233.

(Z)-2-Benzyl-3-(3,5-difluorobenzylidene)isoindolin-1-one ***(3g)***. Brown solid, 183 mg, 90% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 109−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.13−7.08 (m, 3H), 6.73−6.69 (m, 1H), 6.59−6.57 (m, 2H), 6.53 (s, 1H), 6.50 (d, J = 6.0 Hz, 2H), 4.93 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 162.2 (dd, $^1J_{C-F}$ = 248.5 Hz, $^4J_{C-F}$ = 12.9 Hz, 2C), 138.0, 137.8, 136.2, 135.6, 132.4, 129.6, 128.2, 128.0, 126.9, 125.8, 123.7, 119.5, 112.7, 112.6, 112.5, 112.5, 104.4, 102.8 (t, $^3J_{C-F}$ = 24.4 Hz), and 44.9 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{22}H_{16}F_2NO^+$, 348.1194; found, 348.1131.

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

(Z)-2-Benzyl-3-(2-phenylethylidene)isoindolin-1-one (**3h**). Light yellow solid, 69 mg, 36% yield; R_f = 0.5 (15% ethyl acetate/*n*-hexane), mp 97−99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.1 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.33 (td, J = 14.1, 6.7 Hz, 5H), 7.27 (s, 1H), 7.16−7.13 (m, 4H), 6.37 (s, 1H), 5.31 (s, 2H), 3.92 (s, 2H); 13C NMR (125 MHz, $CDCl_3$): δ 163.6, 141.2, 137.4, 136.9, 136.5, 132.5, 129.0, 128.8, 128.3, 128.3, 127.2, 127.1, 126.5, 126.0, 125.5, 124.6, 108.1, 46.5, and 39.4 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{20}NO^+$, 326.1539; found, 326.1476.

(Z)-2-Benzyl-3-(4-methylbenzylidene)isoindolin-1-one (**3i**).[24b] Yellow solid, 119 mg, 62% yield; R_f = 0.5 (15% ethyl acetate/*n*-hexane), mp 100−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.53−7.50 (m, 1H), 7.09−7.04 (m, 5H), 6.98 (d, J = 8.5 Hz, 2H), 6.70 (s, 1H), 6.58 (d, J = 7 Hz, 2H), 4.95 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 138.6, 137.2, 136.9, 134.1, 132.0, 131.5, 129.5, 128.9, 128.6, 128.1, 127.9, 126.7, 126.5, 123.4, 119.4, 107.7, 44.8, and 21.3 ppm.

(Z)-2-Benzyl-5-methoxy-3-(thiophen-3-ylmethylene)-isoindolin-1-one (**3j**). Brown solid, 166 mg, 77% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 119−121 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.22 (q, J = 3.0 Hz, 1H), 7.17−7.15 (m, 1H), 7.12−7.10 (m, 3H), 6.91 (d, J = 3.0 Hz, 1H), 6.79 (d, J = 5.0 Hz, 1H), 6.68−6.66 (m, 2H), 6.43 (s, 1H), 4.98 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 160.9, 137.0, 134.9, 134.7, 131.1, 129.5, 129.3, 128.1, 126.7, 126.2, 125.0, 124.1, 120.8, 120.7, 105.8, 100.9, 55.8, and 44.8 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{21}H_{18}NO_2S^+$, 348.1053; found, 348.0991.

(Z)-2-Benzyl-3-(4-(tert-butyl)benzylidene)-5-methoxyi-soindolin-1-one (**3k**). White solid, 158 mg, 64% yield; R_f = 0.7 (15% ethyl acetate/*n*-hexane), mp 144−146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 8.5 Hz, 1H), 7.38 (s, 1H), 7.23 (d, J = 8.5 Hz, 2H), 7.17 (dd, J = 8.5, 2.0 Hz, 1H), 7.07 (d, J = 6.5 Hz, 1H), 7.02 (t, J = 7.2 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 6.58 (s, 1H), 6.49 (d, J = 7.5 Hz, 2H), 4.93 (s, 2H), 3.92 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 160.8, 150.4, 137.0, 134.0, 131.7, 131.3, 129.6, 129.4, 127.9, 126.6, 126.3, 124.7, 120.7, 120.7, 106.7, 105.7, 55.8, 45.0, 34.6, and 31.3 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{27}H_{28}NO_2^+$, 398.2115; found, 398.2061.

(Z)-2-Benzyl-3-(4-fluorobenzylidene)-5-methoxyisoindo-lin-1-one (**3l**). White solid, 170 mg, 75% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 137−139 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.19−7.16 (m, 1H), 7.08 (d, J = 7.5 Hz, 3H), 6.99−6.96 (m, 2H), 6.91−6.88 (m, 2H), 6.56 (d, J = 6.0 Hz, 2H), 6.51 (s, 1H), 4.88 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 162.1 (d, $^1J_{C-F}$ = 246.1 Hz), 161.1, 136.8, 134.6, 131.3 (d, $^2J_{C-F}$ = 33.5 Hz), 131.2, 130.7, 129.7, 128.8, 128.2, 127.4, 127.0, 126.8, 126.1, 120.9, 120.8, 114.9, 114.8, 105.9, 105.3, 55.9, and 45.1 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{19}FNO_2^+$, 360.1394; found, 360.1466.

(Z)-3-(4-Fluorobenzylidene)-2-phenylisoindolin-1-one (**3m**).[28a] White solid, 168 mg, 87% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 170−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.13−7.10 (m, 3H), 7.08−7.06 (m, 2H), 6.82 (q, J = 4.8 Hz, 2H), 6.77 (s, 1H), 6.63−6.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 161.4 (d, $^1J_{C-F}$ = 246.1 Hz), 138.5, 135.7, 134.5, 132.5, 130.7 (d, $^2J_{C-F}$ = 33.5 Hz), 129.6 (d, $^3J_{C-F}$ = 13.0 Hz), 129.3, 128.2, 127.7, 127.2, 126.9, 123.9, 119.3, 114.2, 114.1, and 106.3 ppm.

(Z)-3-Benzylideneisoindolin-1-one (**3n**).[28a,32,33] Yellow solid, 110 mg, 82% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 177−179 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.65−7.62 (m, 1H), 7.53−7.42 (m, 5H), 7.33−7.30 (m, 1H), 6.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 138.2, 134.9, 133.0, 132.2, 129.2, 129.2, 128.7, 128.4, 127.7, 123.5, 119.8, and 105.9 ppm.

(Z)-2-Benzyl-3-(4-methoxybenzylidene)isoindolin-1-one (**3o**).[24b] Yellow solid, 157 mg, 78% yield; R_f = 0.5 (15% ethyl acetate/*n*-hexane), mp 110−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.61−7.58 (m, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.08 (q, J = 6.7 Hz, 3H), 7.01 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 7.5 Hz, 2H), 6.68 (s, 1H), 6.61 (d, J = 7.0 Hz, 2H), 4.96 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 159.0, 138.6, 137.0, 133.9, 132.0, 130.9, 128.8, 128.0, 127.9, 126.8, 126.7, 126.4, 123.4, 119.3, 113.4, 107.5, 55.3, and 44.9 ppm.

(Z)-3-(4-(tert-Butyl)benzylidene)isoindolin-1-one (**3p**).[28a] Yellow solid, 184 mg, 83% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 197−199 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 6.54 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 151.0, 138.2, 132.2, 132.1, 129.0, 128.6, 128.2, 128.1, 126.2, 123.5, 119.7, 105.9, 34.7, and 31.2 ppm.

(Z)-3-(2-Methoxybenzylidene)isoindolin-1-one (**3q**).[28a] Yellow solid, 143 mg, 71% yield; R_f = 0.5 (15% ethyl acetate/*n*-hexane), mp 154−156 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.77 (dd, J = 21.9, 7.5 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.0 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.26−7.23 (m, 1H), 6.98−6.90 (m, 2H), 6.56 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 156.2, 138.1, 132.7, 131.8, 130.1, 129.1, 128.7, 123.6, 123.2, 121.1, 119.6, 111.3, 102.0, 55.6, and 29.4 ppm.

(Z)-3-(4-Methoxybenzylidene)isoindolin-1-one (**3r**).[28a] White solid, 104 mg, 52% yield; R_f = 0.5 (15% ethyl acetate/*n*-hexane), mp 195−197 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.86 (d, J = 7.0 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 6.50 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 159.3, 138.5, 132.2, 131.7, 129.9, 128.9, 128.6, 127.6, 123.6, 119.7, 114.8, 106.1, and 55.5 ppm.

(Z)-3-(4-Pentylbenzylidene)isoindolin-1-one (**3s**). White solid, 182 mg, 78% yield; R_f = 0.7 (15% ethyl acetate/*n*-hexane), mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.88 (d, J = 7.0 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.63−7.60 (m, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 2.64 (t, J = 7.5 Hz, 2H), 1.66−1.63 (m, 2H), 1.36 (d, J = 4.0 Hz, 4H), 0.93−0.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 142.9, 138.4, 132.5, 132.4, 132.2, 129.4, 129.0, 128.7, 128.5, 123.6, 119.8, 106.3, 35.8, 31.6, 31.1, 22.6, and 14.1 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{22}NO^+$, 292.1696; found, 292.1761.

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

*(Z)-3-(4-Bromobenzylidene)isoindolin-1-one (**3t**).*[28a] White solid, 202 mg, 84% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 220−222 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.78−7.75 (m, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.55 (q, J = 7.9 Hz, 3H), 7.34 (d, J = 8.5 Hz, 2H), 6.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 138.4, 138.2, 134.0, 133.6, 132.5, 132.5, 130.2, 130.0, 129.5, 128.7, 123.8, 121.7, 119.9, and 104.7 ppm.

*(Z)-3-(4-Methylbenzylidene)isoindolin-1-one (**3u**).*[28a] Yellow solid, 111 mg, 59% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 200−202 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.43−7.40 (m, 1H), 7.28 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.44 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 138.3, 137.7, 132.3, 132.1, 132.0, 129.9, 128.9, 128.6, 128.4, 123.5, 119.7, 106.2, and 21.3 ppm.

*(Z)-3-Benzylidene-2-(tert-butyl)isoindolin-1-one (**3v**).*[28c,31] White gel, 146 mg, 80% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 7.5 Hz, 1H), 7.43−7.37 (m, 5H), 7.31 (t, J = 7.5 Hz, 1H), 7.16−7.13 (m, 1H), 6.99 (s, 1H), 6.83 (d, J = 7.5 Hz, 1H), 1.85 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 137.4, 136.3, 135.4, 131.0, 131.0, 129.5, 128.7, 128.6, 127.6, 123.0, 122.6, 114.5, 57.5, and 30.5 ppm.

*(Z)-2-(tert-Butyl)-3-(4-butylbenzylidene)isoindolin-1-one (**3w**).* Light Yellow gel, 171 mg, 78% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 7.5 Hz, 1H), 7.33−7.28 (m, 3H), 7.23 (t, J = 8.0 Hz, 2H), 7.18−7.15 (m, 1H), 6.98 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 2.68 (t, J = 7.5 Hz, 2H), 1.85 (s, 9H), 1.67 (t, J = 7.5 Hz, 2H), 1.42−1.38 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 142.6, 137.2, 135.6, 133.5, 131.1, 131.1, 129.5, 128.9, 128.6, 123.2, 122.7, 114.9, 57.6, 35.5, 33.7, 30.7, 22.5, and 14.1 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{28}NO^+$, 334.2165; found, 334.2157.

*(Z)-3-(4-(tert-Butyl)benzylidene)-2-phenylisoindolin-1-one (**3x**).*[28a] Pale yellow solid, 191 mg, 89% yield; R_f = 0.5 (15% ethyl acetate/*n*-hexane), mp 128−130 °C; ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 14.3 Hz, 5H), 6.92 (d, J = 8.6 Hz, 2H), 6.85 (s, 1H), 6.77 (d, J = 8.6 Hz, 2H), 1.22 (s, 9H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 167.8, 149.7, 138.6, 135.8, 134.1, 132.3, 130.5, 129.0, 128.6, 128.0, 127.2, 126.5, 124.0, 123.8, 119.3, 107.7, 34.3, and 31.1 ppm.

*(Z)-2-Benzyl-3-(4-fluorobenzylidene)isoindolin-1-one (**3y**).*[32] White solid, 171 mg, 88% yield; R_f = 0.5 (15% ethyl acetate/*n*-hexane), mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.62−7.60 (m, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.09−7.05 (m, 3H), 6.99−6.96 (m, 2H), 6.90 (t, J = 8.5 Hz, 2H), 6.63 (s, 1H), 6.55 (d, J = 9.0 Hz, 2H), 4.90 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 162.0, (d, $^1J_{C-F}$ = 246.1 Hz), 138.3, 136.6, 134.6, 132.2, 131.2 (d, $^2J_{C-F}$ = 33.0 Hz), 130.4 (d, $^3J_{C-F}$ = 13.5 Hz), 129.1, 128.0, 126.7, 126.0, 123.5, 119.4, 114.9, 114.7, 106.2, and 44.8 ppm.

*(Z)-2-(tert-Butyl)-3-(4-(tert-butyl)benzylidene)isoindolin-1-one (**3z**).* White solid, 188 mg, 86% yield; R_f = 0.7 (15% ethyl acetate/*n*-hexane), mp 100−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.32−7.30 (m, 3H), 7.19−7.6 (m, 1H), 6.97 (t, J = 4.0 Hz, 2H), 1.84 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 151.4, 137.7, 136.1, 133.8, 131.7, 131.6, 129.8, 129.2, 126.2, 123.6, 123.2, 115.3, 58.1, 35.3, 32.0, and 31.2 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{28}NO^+$, 334.2165; found, 334.2136.

*(Z)-3-(4-Methoxybenzylidene)-2-phenylisoindolin-1-one (**3aa**).*[28a] Light yellow solid, 147 mg, 74% yield; R_f = 0.6 (15% ethyl acetate/*n*-hexane), mp 136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.54−7.51 (m, 1H), 7.13−7.09 (m, 5H), 6.78 (d, J = 6.5 Hz, 3H), 6.47 (d, J = 8.5 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 158.5, 138.9, 136.1, 133.2, 132.4, 130.6, 129.0, 128.3, 127.7, 127.2, 126.7, 126.1, 124.0, 119.3, 112.9, 107.8, and 55.3 ppm.

*(Z)-3-(4-Pentylbenzylidene)isoindolin-1-one (**3ab**).*[28a,34] White solid, 160 mg, 72% yield; R_f = 0.7 (15% ethyl acetate/*n*-hexane), mp 143−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.86 (d, J = 7.0 Hz, 1H), 7.77 (d, J = 6.5 Hz, 1H), 7.62 (s, 1H), 7.50 (d, J = 6.5 Hz, 1H), 7.36 (d, J = 6.5 Hz, 2H), 7.24 (d, J = 6.5 Hz, 2H), 6.53 (s, 1H), 2.62 (d, J = 6.5 Hz, 2H), 1.61 (d, J = 7.0 Hz, 2H), 1.37 (d, J = 6.5 Hz, 2H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 143.1, 138.5, 132.7, 132.5, 132.4, 129.6, 129.3, 128.9, 128.6, 123.8, 120.0, 106.4, 35.6, 33.7, 22.6, and 14.2 ppm.

*(Z)-3-Benzylidene-2-phenylisoindolin-1-one (**3ac**).*[28,29] White solid, 99 mg, 55% yield; R_f = 0.5 (10% ethyl acetate/*n*-hexane), mp 194−196 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.08 (dt, J = 9.9, 3.6 Hz, 5H), 6.97 (d, J = 6.7 Hz, 1H), 6.92 (t, J = 7.6 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 6.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 138.6, 135.9, 134.3, 133.5, 132.4, 129.2, 129.1, 128.1, 127.8, 127.2, 126.7, 126.5, 123.9, 119.3, 107.6, and 29.7 ppm.

General Procedure for the Syntheses of (*E*)-*N*-Aryl-4*H*-thiochromen-4-imines (5a−n). 2-Iodobenzothioamide **4a** (200 mg, 0.59 mmol) was put in anhydrous DMF (4 mL), and ligand **L6** (10 mol %, 13 mg, 0.059 mmol), CuI (5 mol %, 7 mg, 0.03 mmol), terminal alkyne (**2a**, 82.1 mg, 0.70 mmol, 88 μL), and K_2CO_3 (1.2 equiv, 98 mg, 0.71 mmol) were added to it. The mixture was heated at 120 °C in a sealed vessel under an argon atmosphere for 12 h. Completion of the reaction was confirmed by TLC, and the reaction mass was cooled to room temperature, followed by the evaporation of DMF under reduced pressure. The crude residue was purified by column chromatography (230−400 mesh silica gel) to give product **5a** using a mixture of ethyl acetate and *n*-hexane (1:19) as the eluent.

*(E)-N-(2-Phenyl-4H-thiochromen-4-ylidene)aniline (**5a**).*[31] Pale Yellow solid, 158 mg, 86% yield; R_f = 0.5 (10% ethyl acetate/*n*-hexane), mp 115−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 5H), 7.41−7.39 (m, 5H), 7.12 (t, J = 7.5 Hz, 1H), 7.01−6.95 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 151.6, 145.1, 137.5, 134.2, 130.3, 130.0, 129.9, 129.3, 128.9, 127.6, 127.5, 126.7, 126.3, 123.1, 120.3, and 115.2 ppm.

*(E)-N-(2-(4-Methoxyphenyl)-4H-thiochromen-4-ylidene)-aniline (**5b**).*[31] Yellow powder, 157 mg, 78% yield; R_f = 0.6 (10% ethyl acetate/*n*-hexane), mp 91−95 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (d, J = 7.0 Hz, 1H), 7.48−7.45 (m, 3H), 7.43−7.36 (m, 4H), 7.10 (d, J = 8.0 Hz, 1H), 6.94−6.88 (m, 5H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 155.5, 151.8, 144.8, 134.3, 130.4, 130.0, 129.9, 129.4, 128.1, 127.6, 127.5, 126.3, 123.1, 120.5, 114.4, 114.1, and 55.5 ppm.

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

*(E)-N-(2-(4-(tert-Butyl)phenyl)-4H-thiochromen-4-ylidene)aniline (**5c**).* Yellow solid, 156 mg, 72% yield; R_f = 0.6 (10% ethyl acetate/*n*-hexane), mp 128−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, J = 7.5 Hz, 1H), 7.48−7.45 (m, 3H), 7.41−7.36 (m, 6H), 7.10−7.07 (m, 1H), 6.98−6.92 (m, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 153.5, 151.8, 145.1, 134.7, 134.4, 130.5, 130.0, 129.4, 127.7, 127.6, 126.5, 126.4, 126.0, 123.1, 120.5, 114.8, 34.9, and 31.2 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{25}H_{24}NS^+$, 370.1624; found, 370.1589.

*(E)-N-(2-(2-Methoxyphenyl)-4H-thiochromen-4-ylidene)-aniline (**5d**).* Yellow solid, 143 mg, 71% yield; R_f = 0.5 (10% ethyl acetate/*n*-hexane), mp 130−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68−8.67 (m, 1H), 7.47−7.43 (m, 3H), 7.34 (t, J = 8.0 Hz, 4H), 7.04 (t, J = 7.5 Hz, 1H), 6.97−6.90 (m, 5H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 155.2, 151.7, 141.8, 135.2, 130.8, 130.2, 130.1, 129.8, 129.1, 127.4, 127.4, 126.2, 126.0, 122.9, 120.7, 120.5, 118.7, 111.5, and 55.6 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{22}H_{18}NOS^+$, 344.1104; found, 344.1079.

*(E)-N-(2-(4-Fluorophenyl)-4H-thiochromen-4-ylidene)-aniline (**5e**).* Yellow crystalline solid, 152 mg, 78% yield; R_f = 0.4 (10% ethyl acetate/*n*-hexane), mp 112−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, J = 7.5 Hz, 1H), 7.48−7.43 (m, 5.4 Hz, 5H), 7.38 (t, J = 7.5 Hz, 2H), 7.11−7.05 (m, 3H), 6.92 (d, J = 8.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8 (d, $^1J_{C-F}$ = 249.8 Hz), 155.2, 151.6, 144.1, 134.0, 133.7, 130.4, 130.2, 129.4, 128.7 (d, $^2J_{C-F}$ = 34.5 Hz), 127.8, 127.6, 126.3, 123.3, 120.4, 116.2, 116.1, and 115.3 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{21}H_{15}FNS^+$, 332.0904; found, 332.0853.

*(E)-N-(2-(Thiophen-3-yl)-4H-thiochromen-4-ylidene)-aniline (**5f**).* Yellow powder, 167 mg, 89% yield; R_f = 0.6 (10% ethyl acetate/*n*-hexane), mp 104−106 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67−8.65 (m, 1H), 7.53 (d, J = 3.0 Hz, 1H), 7.48−7.44 (m, 3H), 7.38 (t, J = 7.5 Hz, 2H), 7.33 (q, J = 3.0 Hz, 1H), 7.15−7.13 (m, 1H), 7.11−7.08 (m, 1H), 7.00 (s, 1H), 6.93 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 151.7, 139.2, 138.6, 133.9, 130.5, 130.1, 129.4, 127.7, 127.6, 127.0, 126.3, 125.3, 123.9, 123.2, 120.5, and 114.0 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{19}H_{14}NS_2^+$, 320.0562; found, 320.0538.

*(E)-N-(2-(p-Tolyl)-4H-thiochromen-4-ylidene)aniline (**5g**).* Yellow solid, 144 mg, 75% yield; R_f = 0.6 (10% ethyl acetate/*n*-hexane), mp 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (d, J = 7.5 Hz, 1H), 7.52−7.42 (m, 3H), 7.37 (t, J = 7.0 Hz, 4H), 7.18 (d, J = 8.0 Hz, 2H), 7.09−7.03 (m, 1H), 6.95−6.92 (m, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 151.6, 145.1, 140.3, 134.6, 134.3, 130.3, 129.9, 129.6, 129.3, 127.6, 127.5, 126.5, 126.2, 123.0, 120.4, 114.6, 77.3, 77.0, 76.7, and 21.3 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{22}H_{18}NS^+$, 328.1154; found, 328.1102.

*(E)-N-(2-(4-Pentylphenyl)-4H-thiochromen-4-ylidene)-aniline (**5h**).* Brown gel, 176 mg, 78% yield; R_f = 0.6 (10% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (d, J = 7.0 Hz, 1H), 7.48−7.45 (m, 3H), 7.37−7.35 (m, 4H), 7.19 (d, J = 8.0 Hz, 2H), 7.09−7.06 (m, 1H), 6.96−6.92 (m, 3H), 2.60 (t, J = 7.7 Hz, 2H), 1.37−1.29 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 145.4, 134.9, 134.4, 130.1, 129.4, 129.1, 127.7, 127.6, 126.6, 126.4, 123.1, 120.5, 114.7, 35.7, 31.5, 31.0, 22.6, and 14.1 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{26}H_{26}NS^+$, 384.1780; found, 384.1771.

*(E)-N-(2-(2-(Trifluoromethyl)phenyl)-4H-thiochromen-4-ylidene)aniline (**5i**).* Yellow solid, 173 mg, 77% yield; R_f = 0.4 (10% ethyl acetate/*n*-hexane), mp 114−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71−8.70 (m, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.56−7.41 (m, 6H), 7.31 (t, J = 7.5 Hz, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.5 Hz, 2H), 6.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.2, 142.2, 135.7, 134.4, 131.6, 131.3, 130.1, 129.3, 129.2, 127.8, 127.6, 126.6 (q, J_{C-F} = 19.0 Hz), 125.9, 123.1, 120.2, and 118.8 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{22}H_{15}F_3NS^+$, 382.0872; found, 382.0858.

*(E)-N-(2-(4-Methoxy-2-methylphenyl)-4H-thiochromen-4-ylidene)aniline (**5j**).* Orange solid, 170 mg, 81% yield; R_f = 0.4 (10% ethyl acetate/*n*-hexane), mp 110−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (dd, J = 7.5, 1.8 Hz, 1H), 7.49−7.42 (m, 3H), 7.34−7.31 (m, 2H), 7.21 (d, J = 8.5 Hz, 1H), 7.04−7.02 (m, 1H), 6.88 (d, J = 7.5 Hz, 2H), 6.74−6.72 (m, 2H), 6.57 (s, 1H), 3.79 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 155.1, 151.7, 145.3, 137.7, 135.2, 130.5, 130.4, 130.0, 129.7, 129.3, 127.7, 127.6, 126.1, 123.0, 120.4, 118.3, 116.3, 111.4, 55.4, and 20.4 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{23}H_{20}NOS^+$, 358.1260; found, 358.1237.

*(E)-N-(2-(5-Methoxynaphthalen-2-yl)-4H-thiochromen-4-ylidene)aniline (**5k**).* Brown solid, 183 mg, 79% yield; R_f = 0.5 (10% ethyl acetate/*n*-hexane), mp 130−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (d, J = 7.0 Hz, 1H), 7.92 (s, 1H), 7.72 (dd, J = 20.7, 8.8 Hz, 2H), 7.50−7.47 (m, 4H), 7.41−7.38 (m, 2H), 7.18−7.16 (m, 1H), 7.11 (d, J = 12.0 Hz, 3H), 6.98 (d, J = 7.5 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 155.4, 151.7, 145.3, 135.4, 134.4, 132.5, 130.5, 130.2, 130.1, 129.4, 128.5, 127.7, 127.7, 127.6, 126.4, 126.3, 124.4, 123.2, 120.6, 119.9, 115.0, 105.7, and 55.5 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{26}H_{20}NOS^+$, 394.1260; found, 394.1229.

*(E)-N-(2-(2,4,5-Trimethylphenyl)-4H-thiochromen-4-ylidene)aniline (**5l**).* Yellow solid, 157 mg, 75% yield; R_f = 0.6 (10% ethyl acetate/*n*-hexane), mp 98−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71−8.70 (m, 1H), 7.49−7.47 (m, 2H), 7.46−7.43 (m, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.05−6.99 (m, 3H), 6.87 (d, J = 7.5 Hz, 2H), 6.58 (s, 1H), 2.23 (s, 6H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 151.6, 145.4, 137.9, 135.0, 134.4, 134.1, 132.9, 132.0, 130.2, 130.0, 129.9, 129.2, 127.6, 127.5, 126.0, 122.8, 120.2, 117.9, 19.4, 19.3, and 19.0 ppm; HRMS m/z: $[M + H]^+$ calcd for $C_{24}H_{22}NS^+$, 356.1467; found, 356.1452.

*(E)-N-(2-(4-Butylphenyl)-4H-thiochromen-4-ylidene)-aniline (**5m**).* Orange solid, 174 mg, 80% yield; R_f = 0.6 (10% ethyl acetate/*n*-hexane), mp 84−86 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, J = 7.0 Hz, 1H), 7.48−7.44 (m, 3H), 7.38 (t, J = 7.5 Hz, 4H), 7.19 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 7.5 Hz, 1H), 6.97−6.93 (m, 3H), 2.62 (t, J = 7.5 Hz, 2H), 1.38−1.27 (m, 4H), 0.94−0.91 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 151.6, 145.3, 145.2, 134.8, 134.3, 130.3, 129.9, 129.3, 129.0, 127.5, 127.5, 126.5, 126.2, 123.0, 120.4, 114.6, 35.3, 33.4, 22.3, and 13.9 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{25}H_{24}NS^+$, 370.1624; found, 370.1615.

*(E)-N-(2-(4-(tert-Butyl)phenyl)-4H-thiochromen-4-ylidene)-2-chloroaniline (**5n**).* Oily liquid, 168 mg, 78% yield; R_f = 0.5 (10% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (d, J = 9.0 Hz, 1H), 7.51−7.47 (m, 3H), 7.44−7.39 (m, 5H), 7.25−7.22 (m, 1H), 7.01 (t, J = 7.3 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 153.6, 148.6, 146.0, 134.6, 134.5, 130.1, 130.1, 129.9, 127.8, 127.7, 127.5, 126.5, 126.3, 126.0, 125.1, 123.9, 121.7, 114.8, 34.7, and 31.1 ppm. HRMS m/z: $[M + H]^+$ calcd for $C_{25}H_{23}ClNS^+$, 404.1234; found, 404.1225.

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

General Procedure for the Syntheses of Dialkynes (6a−d). A round-bottom flask was charged with 1-(*tert*-butyl)-4-ethynylbenzene (150 mg, 0.87 mmol), CuI (5 mol %, 9 mg, 0.04 mmol), **L6** (10 mol %, 20 mg, 0.094 mmol), and K_2CO_3 (1.2 equiv, 155 mg, 1.12 mmol). The mixture was dissolved in anhydrous DMF (2−3 mL) and vigorously stirred for 4.0−5.0 h under a closed vessel. Completion of the reaction was confirmed by TLC, and the reaction mixture was subjected to evaporation of DMF under reduced pressure. The crude residue was purified by column chromatography (230−400 mesh silica gel) to give product **6a** using *n*-hexane as the eluent.

*1,4-Bis(4-(tert-butyl)phenyl)buta-1,3-diyne (**6a**).*[35] White solid, 101 mg, 74% yield; R_f = 0.4 (*n*-hexane) mp 180−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 8.0 Hz, 4H), 7.35 (d, J = 7.0 Hz, 4H), 1.30 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.5, 132.2, 125.4, 118.7, 81.4, 73.4, 34.8, and 31.0 ppm.

*1,4-Bis(thiophen-3-yl)buta-1,3-diyne (**6b**).*[35] White solid, 83 mg, 56% yield; R_f = 0.5 (5% ethyl acetate/*n*-hexane), mp 110−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 3.0 Hz, 2H), 7.29−7.27 (m, 2H), 7.17 (d, J = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.2, 130.1, 125.5, 120.8, 76.5, and 73.4 ppm.

*1,4-Bis(4-methylphenyl)buta-1,3-diyne (**6c**).*[35] White solid, 103 mg, 69% yield; R_f = 0.6 (*n*-hexane), mp 180−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 4H), 7.11 (d, J = 7.5 Hz, 4H), 2.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2 132.1, 128.9, 118.5, 81.2, 73.18, and 21.3 ppm.

*1,4-Diphenylbuta-1,3-diyne (**6d**).*[35] White solid, 130 mg, 88% yield; R_f = 0.7 (*n*-hexane), mp 82−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 6.5 Hz, 4H), 7.39−7.34 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.4, 129.1, 128.4, 121.7, 81.5, and 73.9 ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03003.

^{1}H and ^{13}C NMR of all the developed compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Vinod K. Tiwari − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India;* orcid.org/0000-0001-9244-8889; Email: Tiwari_chem@yahoo.co.in, Vinod.Tiwari@bhu.ac.in

Authors

Sumit K. Singh − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India*

Mangal S. Yadav − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India*

Anoop S. Singh − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India*

Anand K. Agrahari − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India*

Nidhi Mishra − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India*

Sunil Kumar − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c03003

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors sincerely thank the Council of Scientific & Industrial Research (CSIR), New Delhi (Scheme no.: 02(0345)/19/EMR-II) and Institute of Eminence (IOE), Banaras Hindu University (BHU), Varanasi, for the financial support. The authors gratefully acknowledge the Indian Institute of Technology, Kanpur and CISC, Department of Chemistry, Institute of Science, BHU, for providing spectroscopic studies of the developed molecules and BHU for the basic infrastructure. M.S.Y. and A.K.A. acknowledge the CSIR for SRF, and S.K.S. thanks the University Grants Commission (UGC) for JRF.

■ REFERENCES

(1) (a) Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. First Total Synthesis of Fumaridine. *Tetrahedron* **2003**, *59*, 6615−6619. (b) Hari Balakrishnan, M.; Mannathan, S. Palladium/Copper-Catalyzed Denitrogenative Alkylidenation and ortho-Alkynylation Reaction of 1,2,3-Benzotriazin-4(3H)-ones. *Org. Lett.* **2020**, *22*, 542−546.

(2) (a) Kato, Y.; Takemoto, M.; Achiwa, K. Prostanoids and Related Compounds. VII. Synthesis and Inhibitory Activity of 1-Isoindolinone Derivatives Possessing Inhibitory Activity against Thromboxane A2 Analog (U-46619)-Induced Vasoconstriction. *Chem. Pharm. Bull.* **1999**, *47*, 529−535. (b) Kato, Y.; Takemoto, M.; Achiwa, K. Prostanoids and related compounds. VI. Synthesis of Isoindolinone Derivatives Possessing Inhibitory Activity for Thromboxane A2 analog (U-46619)-induced Vasoconstriction. *Chem. Pharm. Bull.* **1993**, *41*, 2003.

(3) (a) Linden, M.; Hadler, D.; Hofmann, S. Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Tolerability of a New Isoindoline Derivative (DN-2327) in Generalized Anxiety. *Hum. Psychopharmacol.* **1997**, *12*, 445−452. (b) Wang, E. C.; Chen, H. F.; Feng, P. K.; Lin, Y. L.; Hsu, M. K. A New Synthesis of 3-Alkyl-1-Isoindolinones. *Tetrahedron* **2002**, *43*, 163−165.

(4) Couture, A.; Deniau, E.; Grandclaudon, P. An Efficient One-Pot Synthesis of 3-(Aryl and Alkyl) methylene-1H-isoindolin-1-ones via Aryne Cyclization and Horner Reaction of o-(and m-) Halogens-N-phosphorylmethylbenzamide Derivatives. *Tetrahedron* **1997**, *53*, 10313−10330.

(5) Couture, A.; Deniau, E.; Grandclaudon, P.; Rybalko, R. H.; Leonce, S.; Pfeifferc, B.; Renardc, P. Synthesis and Biological Evaluation of Aristolactams. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557−3559.

(6) Enders, D.; Braig, V.; Raabe, G. Asymmetric Synthesis of 3-Aryl-substituted 2,3- Dihydro-1H-isoindol-1-ones. *Can. J. Chem.* **2001**, *79*, 1528−1535.

(7) (a) Kato, Y.; Ebike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. Synthesis and Inhibitory Activity of Isoindolinone Derivatives On Thromboxane A_2 Analog (U-46619)-Induced Vaso-contraction. *Chem. Pharm. Bull.* **1990**, *38*, 2060−2062. (b) Rys, V.; Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. A concise benzotriazolyl-mediated synthesis of 9-methoxycepharanone A. *Tetrahedron* **2005**, *61*, 665−671. (c) Bose, A.; Korotzer, A.; Gommoll, C.; Li, D. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the Treatment of Generalized Anxiety Disorder. *Depression Anxiety* **2008**, *25*, 854−861.

(8) (a) Weinstock, J.; Heible, J. P.; Wilson, J. W. The chemistry and pharmacology of 3-benzazepine derivatives. *Drugs of the Future* **1985**, *10*, 645-697. (b) Gogoi, A.; Guin, S.; Rout, S. K.; Majji, G.; Patel, B. K. A Cu-Catalysed Synthesis of Substituted 3-Methyleneisoindolin-1-one. *RSC Adv.* **2014**, *4*, 59902−59907.
(9) Blaskó, G.; Gula, D. J.; Shamma, M. The Phthalideisoquinoline Alkaloids. *J. Nat. Prod.* **1982**, *45*, 105−122.
(10) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. A concise first total synthesis of narceine imide. *Org. Biomol. Chem.* **2007**, *5*, 1466−1471.
(11) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. A brief total synthesis of fumaramidine. *Tetrahedron* **2006**, *62*, 2917−2921.
(12) Sharma, M.; Moniot, J. L. Revised structure for Fumaridine and Fumaramine. *J. Chem. Soc., Chem. Commun.* **1975**, *3*, 89−90.
(13) Speck, K.; Magauer, T. The chemistry of isoindole natural products. *Beilstein J. Org. Chem.* **2013**, *9*, 2048−2078.
(14) Pigeon, P.; Decroix, B. Benzothienoindolizidines via Intramolecular Aryl Radical Cyclization or Palladium Catalyzed Cyclization. *Tetrahedron Lett.* **1996**, *37*, 7707−7710.
(15) Yoo, M.; Park, T. H.; Yoo, M.; Kim, Y.; Lee, J.-Y.; Lee, K. M.; Ryu, S. E.; Lee, B. I.; Jung, K.-Y.; Park, C. H. Synthesis and Structure-Activity Relationships of Aristoyagonine Derivatives as Brd4 Bromodomain Inhibitors with X-ray Co-Crystal Research. *Molecules* **2021**, *26*, 1686.
(16) Botero Cid, H. M.; Tränkle, C.; Baumann, K.; Pick, R.; Mies-Klomfass, E.; Kostenis, E.; Mohr, K.; Holzgrabe, U. Structure-activity relationships in a series of bisquaternary bisphthalimidine derivatives modulating the muscarinic M(2)-receptor allosterically. *J. Med. Chem.* **2000**, *43*, 2155−2164.
(17) (a) Suzuki, M.; Uchiumi, M.; Murasaki, M. A comparative study of the psychological effects of DN.2327, a partial benzodiazepine agonist, and aiprazolam. *Psychopharmacology* **1995**, *121*, 442−450. (b) Pan, J.; Xu, Z.; Zeng, R.; Zou, J. Copper(II)-Catalyzed Tandem Synthesis of Substituted 3-Methyleneisoindolin-1-ones. *Chin. J. Chem.* **2013**, *31*, 1022−1026.
(18) Luque-Agudo, V.; Albarrán-Velo, J.; Fernández-Bolaños, J. G.; López, O.; Light, M. E.; Padrón, J. M.; Lagunes, I.; Román, E.; Serrano, J. A.; Gil, M. V. Synthesis and Antiproliferative Activity of Sulfa-Michael Adducts and Thiochromenes Derived from Carbohydrates. *New J. Chem.* **2017**, *41*, 3154−3162.
(19) Ito, C.; Isobe, Y.; Kijima, H.; Kiuchi, Y.; Ohtsuki, H.; Kawamura, R.; Tsuchida, K.; Higuchi, S. The anti-emetic activity of GK-128 in Suncus murinus. *Eur. J. Pharmacol.* **1995**, *285*, 37−43.
(20) (a) Singh, V. P.; Yan, J.; Poon, J.-F.; Gates, P. J.; Butcher, R. J.; Engman, L. Chain-Breaking Phenolic 2,3-Dihydrobenzo[b]-selenophene Antioxidants: Proximity Effects and Regeneration Studies. *Chem.—Eur. J.* **2017**, *23*, 15080−15088. (b) Viglianisi, C.; Amorati, R.; Di Pietro, L.; Menichetti, S. A Straightforward Route to Potent Phenolic Chain-breaking Antioxidants by Acid-promoted Transposition of 1,4-Benzo[b]oxathiines to Dihydrobenzo[b]-thiophenes. *Chem.—Eur. J.* **2015**, *21*, 16639−16645.
(21) Suresh, L.; Sagar Vijay Kumar, P.; Poornachandra, Y.; Ganesh Kumar, C.; Chandramouli, G. V. P.; Chandramouli, G. V. P. An Efficient One-Pot Synthesis of Thiochromeno[3,4-d]pyrimidines Derivatives: Inducing ROS Dependent Antibacterial and Anti-biofilm Activities. *Bioorg. Chem.* **2016**, *68*, 159−165.
(22) Chen, Y.; Zhang, Q.; Zhang, B.; Xia, P.; Xia, Y.; Yang, Z.-Y.; Kilgore, N.; Wild, C.; Morris-Natschke, S. L.; Lee, K.-H. Anti-AIDS Agents. Part 56: Synthesis and Anti-HIV Activity of 7-Thia-di-O-(−)-Camphanoyl-(+)-cis-Khellactone (7-thia-DCK) Analogs. *Bioorg. Med. Chem.* **2004**, *12*, 6383−6387.
(23) (a) Sarkar, S.; Dutta, S.; Dey, R.; Naskar, S. A Novel Approach for Highly Regio- and Stereoselective Synthesis of (Z)-3-Methyleneisoindoline-1-ones in Aqueous Micellar Medium. *Tetrahedron Lett.* **2012**, *53*, 6789−6792. (b) Chatterjee, N.; Sarkar, S.; Pal, R.; Sen, A. K. A Green Approach for the Regio- and Stereo-selective Syntheses of (Z)-3-Methyleneisoindoline-1-ones in Aqueous Medium. *Tetrahedron Lett.* **2013**, *54*, 3748−3751. (c) Kise, N.; Isemoto, S.; Sakurai, T. Electroreductive Intramolecular Coupling of Phthalimides with Aromatic Aldehydes: Application to the Synthesis of Lennoxamine. *J. Org. Chem.* **2011**, *76*, 9856−9860.
(24) (a) Chahdoura, F.; Mallet-Ladeira, S.; Gómez, M. Palladium nanoparticles in glycerol: clear-cut catalyst for one-pot multi-step processes applied in the synthesis of heterocyclic compounds. *Org. Chem. Front.* **2015**, *2*, 312−318. (b) Li, L.; Wang, M.; Zhang, X.; Jiang, Y.; Ma, D. Assembly of Substituted 3-Methyleneisoindolin-1-ones via a CuI/L-Proline-Catalyzed Domino Reaction Process of 2-Bromobenzamides and Terminal Alkynes. *Org. Lett.* **2009**, *11*, 1309−1312.
(25) Flitsch, W.; Peters, H. Wittig-Reaktionen an Imiden. *Tetrahedron Lett.* **1969**, *10*, 1161.
(26) (a) Mishra, N.; Singh, A. S.; Agrahari, A. K.; Singh, S. K.; Singh, M.; Tiwari, V. K. Synthesis of Benz-Fused Azoles via C-Heteroatom Coupling Reactions Catalyzed by Cu(I) in the Presence of Glycosyltriazole Ligands. *ACS Comb. Sci.* **2019**, *21*, 389−399. (b) Mishra, A.; Mishra, N.; Tiwari, V. K. Carbohydrate-based Organocatalysts: Recent Developments and Future Perspectives. *Curr. Org. Synth.* **2016**, *13*, 176−219. (c) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. Cu-Catalyzed Click Reaction in Carbohydrate Chemistry. *Chem. Rev.* **2016**, *116*, 3086−3240. (d) Agrahari, A. K.; Bose, P.; Jaiswal, M. K.; Rajkhowa, S.; Singh, A. S.; Hotha, S.; Mishra, N.; Tiwari, V. K. Cu(I)-Catalyzed Click Chemistry in Glycoscience and Their Diverse Applications. *Chem. Rev.* **2021**, *121*, 7638−7957.
(27) (a) Thakur, K. G.; Ganapathy, D.; Sekar, G. D-Glucosamine as a Green Ligand for Copper Catalyzed Synthesis of Primary Aryl Amines from Arylhalides and Ammonia. *Chem. Commun.* **2011**, *47*, 5076−5078. (b) Singh, N.; Pandey, J.; Tripathi, R. P. D-Glucosamine, a Natural Aminosugar as Organocatalyst for an Ecofriendly Direct Aldol Reaction of Ketones with Aromatic Aldehydes in Water. *Catal. Commun.* **2008**, *9*, 743−746.
(28) (a) Hazarika, D.; Phukan, P. Copper-Catalyzed Stereoselective Domino Synthesis of (Z)-3-Methyleneisoindolin-1-one. *Chem. Sel.* **2018**, *3*, 2474−2478. (b) Griesbeck, A. G.; Neudörfl, J.-M.; Goldfuss, B.; Molitor, S. Synthesis of 3-Benzylated Isoindolinones by Photoredox Decarboxylation of Arylacetates in the Presence of N -Benzylphthalimide: Conductivity as a Kinetic Tool. *ChemPhotoChem* **2017**, *1*, 355−362. (c) Munoz, S. B.; Aloia, A. N.; Moore, A. K.; Papp, A.; Mathew, T.; Fustero, S.; Olah, G. A.; Surya Prakash, G. K. Synthesis of 3-Substituted Isoindolin-1-ones via a Tandem Desilylation-cross-Coupling Hydroamidation Sequence Under Aqueous Phase-Transfer Conditions. *Org. Biomol. Chem.* **2016**, *14*, 85−92.
(29) Kanazawa, C.; Terada, M. Dichotomous Control of (E)/(Z)Geometry in Intramolecular Cyclization of o-Alkynylbenzamide Derivatives Catalyzed by Organic Superbase P4-tBu in the Presence/Absence of Water. *Chem.—Asian J.* **2019**, *4*, 1668−1672.
(30) (a) Cheng, D.; Gan, F.; Qian, W.; Bao, W. D-Glucosamine- A Natural Ligand for the N-Arylation of Imidazoles with Aryl and Heteroaryl Bromides Catalyzed by CuI. *Green Chem.* **2008**, *10*, 171−173. (b) Ge, X.; Chen, X.; Qian, C.; Zhou, S. Combined Experimental/theoretical Study of D-Glucosamine Promoted Ullmann-type C−N Coupling Catalyzed by Copper(I): Does Amino Really Count? *RSC Adv.* **2016**, *6*, 29638−29645. (c) Wei, J. J.; Song, W. B.; Zhu, Y. F.; Wei, B. L.; Xuan, L. J. N,N-Dimethyl-D-glucosamine as an efficient ligand for copper-catalyzed Ullmann-type coupling of N-H heterocycles with aryl halides. *Tetrahedron* **2018**, *74*, 19−27.
(31) Ma, Y.-G.; Huang, M.-Q.; Liu, Z.; Liu, J.-Q.; Wang, X.-S. Synthesis of Substituted 4H-Thiochromen-4-imines via Copper-Catalyzed Cyclization Cascades of o-Bromobenzothioamides with Terminal Alkynes. *J. Org. Chem.* **2018**, *83*, 9504−9509.
(32) Zhang, L.; Zhang, Y.; Wang, X.; Shen, J. Efficient Synthesis of a (Z)-3-Methyleneisoindolin-1-one Library Using $Cu(OAc)_2{\cdot}H_2O$/DBU under Microwave Irradiation. *Molecules* **2013**, *18*, 654−665.
(33) Cao, H.; McNamee, L.; Alper, H. Syntheses of Substituted 3-Methyleneisoindolin-1-ones By a Palladium-Catalyzed Sonogashira Coupling-Carbonylation-Hydroamination Sequence in Phosphonium Salt-Based Ionic liquids. *Org. Lett.* **2008**, *10*, 5281−5284.

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138

(34) Irudayanathan, F. M.; Noh, J.; Choi, J.; Lee, S. Copper-Catalyzed Selective Synthesis of Isoindolin-1-ones and Isoquinolin-1-ones from the Three-Component Coupling of 2-Halobenzoic Acid, Alkynylcarboxylic Acid and Ammonium Acetate. *Adv. Synth. Catal.* **2014**, *356*, 3433−3442.
(35) Singh, M.; Singh, A. S.; Mishra, N.; Agrahari, A. K.; Tiwari, V. K. Benzotriazole as an Efficient Ligand in Cu-Catalyzed Glaser Reaction. *ACS Omega* **2019**, *4*, 2418−2424.

https://doi.org/10.1021/acsomega.1c03003
ACS Omega 2021, 6, 21125−21138