JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

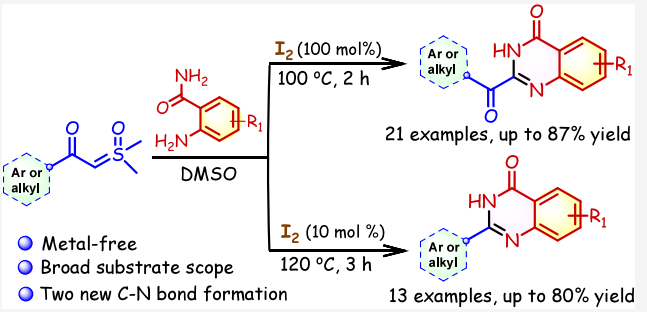
I_2-Promoted Chemoselective Annulative Coupling of 2-Aminobenzamides with Sulfoxonium Ylides: Easy Access to Quinazolinones

Ajay Kant Gola, Naveen Kumar, and Satyendra Kumar Pandey*

Cite This: https://doi.org/10.1021/acs.joc.4c01354 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A flexible and metal-free synthetic approach for synthesizing 2-benzoyl quinazolinones and 2-aryl quinazolinones via molecular iodine-mediated annulative coupling of sulfoxonium ylides with 2-aminobenzamides has been disclosed. The method demonstrates remarkable chemoselectivity and efficiency, leading to high yields of 2-benzoyl quinazolinones and 2-aryl quinazolinones under optimized conditions. The broad substrate scope, scalability, and practical utility were highlighted through diverse applications, including gram-scale reactions and the synthesis of biologically significant compounds such as tryptanthrin and the chemo/biosensor derivative.



INTRODUCTION

Nitrogen-containing heterocycles serve as ubiquitous frameworks in numerous natural compounds and functional materials as well as in the pharmaceutical sector.[1] Within this group, quinazolinones are a key structural element commonly found in various naturally occurring alkaloids, showcasing noteworthy pharmacological properties (Figure 1).[2] They have been used for a variety of biological activities, including antifungal, antitubercular, anticancer, antihypertensive, antiviral, and depressive properties.[3] Over the last few decades, numerous synthetic approaches have been developed to synthesize 2-benzoyl quinazolinones[4] and 2-aryl quinazolinones.[5] The predominant approach involves using 2-aminobenzamide and its derivatives as initial reactants in conjunction with aldehydes or similar compounds to synthesize quinazolinones in the presence of metal or nonmetal catalysts (Scheme 1). In 2023, Lin and co-workers developed an elegant method for synthesizing 2-benzoyl quinazolinones by facilitating the ring opening of an epoxide using I_2/DMSO and 2-aminobenzamide.[4a] On the other hand, Deori, Sarma, and co-workers developed a synthetic approach to synthesize 2-aryl quinazolinones using anthranilamide and benzyl alcohol in the presence of the ionic liquid [DDQM][HSO_4], utilizing microwave irradiation.[5a] However, the majority of the approaches require the use of substantial quantities of oxidizing agents (such as *t*-BuOOH, DDQ, $KMnO_4$, $PhI(OAc)_2$, etc.), entail prolonged reaction durations, expensive reagents, limited range of substrates scope, and multistep operations, and result in the generation of significant byproducts.[6−8] Despite considerable advances in their synthesis, the academic and pharmaceutical sectors continue to seek a straightforward synthetic approach for quinazolinones in the quest for bioactive molecules. To our knowledge, no research studies have shown that sulfoxonium ylides may act as both acyl and aryl/alkyl precursors in the synthesis of quinazolinone derivatives.

Recently, sulfoxonium ylides have become increasingly favored as substitutes for diazo compounds in diverse organic

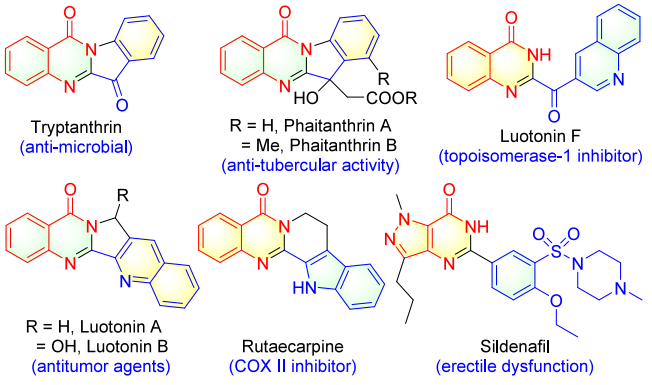
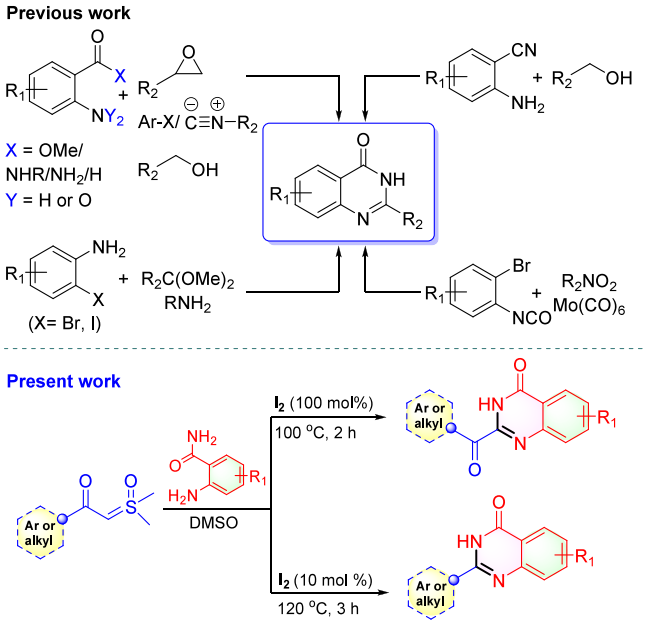


Figure 1. Selected quinazolinone-containing natural products and drug molecules.

Received: May 30, 2024
Revised: July 29, 2024
Accepted: August 13, 2024

Scheme 1. Recent Synthetic Strategies for Quinazolinones



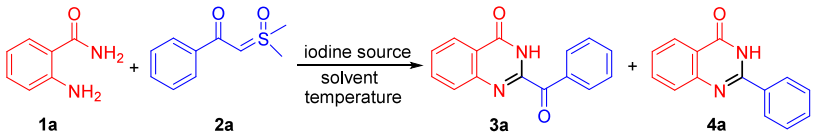
reactions owing to their stability, accessibility, and wide-ranging reactivity.[9] They have been widely utilized as foundational building blocks in the construction of heterocyclic molecules such as indole, pyrrole, furan, quinolone, and pyrimidine, typically relying on the aid of transition metal catalysts.[10] This study aims to showcase the unusual reactivity of sulfoxonium ylides and establish an innovative method for synthesizing quinazolinones without using metal catalysts.

RESULTS AND DISCUSSION

In our ongoing investigation of sulfoxonium ylides chemistry,[11] we hypothesized that the α-carbon could undergo a nucleophilic reaction with electrophilic iodine. This process could potentially initiate the oxidation of an iodo intermediate, leading to the formation of a phenylglyoxal intermediate upon release of DMSO. The subsequent condensation of this intermediate with 2-aminobenzamide would result in the formation of quinazolinone derivatives. To validate our hypothesis, we conducted preliminary investigations utilizing 2-aminobenzamide **1a** and β-ketosulfoxonium ylide **2a** as representative substrates (Table 1). We were pleased to find that using model substrates in DMSO at 60 °C furnished the 2-benzoyl quinazolinone **3a** within 10 h with a 45% yield; however, unexpectedly, this also led to the formation of 2-phenyl quinazolinone **4a** with a 20% yield (entry 2).

The formation of 2-phenyl quinazolinone **4a** suggested a substantial cleavage of the C−C bond within the reaction. This promising outcome motivated us to investigate the reaction in depth to determine the optimal conditions for synthesizing both 2-benzoyl quinazolinone **3a** and 2-phenyl quinazolinone **4a** without using metal catalysts. Assessment of different protic and aprotic solvents at various temperatures demonstrated that the reaction yielded the most favorable outcomes in DMSO compared to alternative solvents in the presence of I_2 (100 mol %) at 100 °C over a period of 2 h (entry 4 vs entries 2−11). In the pursuit of improving the chemoselectivity of the transformation, we further explored various optimization reactions at different temperatures and iodine mol % (entries 12−17). Interestingly, our studies revealed that employing catalytic amounts of iodine (10 mol %) promoted the synthesis of 2-phenyl quinazolinone **4a** in DMSO solvent at 120 °C (entry

Table 1. Optimization[a]



entry	solvent	iodine (x mol %)	temp (°C)[b]	time (h)	yield of **3a** (%)[c]	yield of **4a** (%)[c]
1	DMSO	100	rt	24	0	0
2	DMSO	100	60	10	45	20
3	DMSO	100	80	6	60	30
4	DMSO	100	100	2	86	traces
5	DMSO	100	120	2	82	traces
6	THF	100	100	8	45	traces
7	toluene	100	100	14	35	0
8	CH_3CN	100	100	8	0	40
9	EtOH	100	100	8	15	0
10	H_2O	100	100	8	21	0
11	DMF	100	100	4	30	25
12	DMSO	50	100	4	50	30
13	DMSO	30	100	4	30	45
14	DMSO	10	100	3	traces	72
15	DMSO	10	80	6	18	56
16	DMSO	10	120	3	traces	76
17	CH_3CN	10	120	6	traces	59
18		100	100	2	40	traces
19		10	120	6	traces	traces

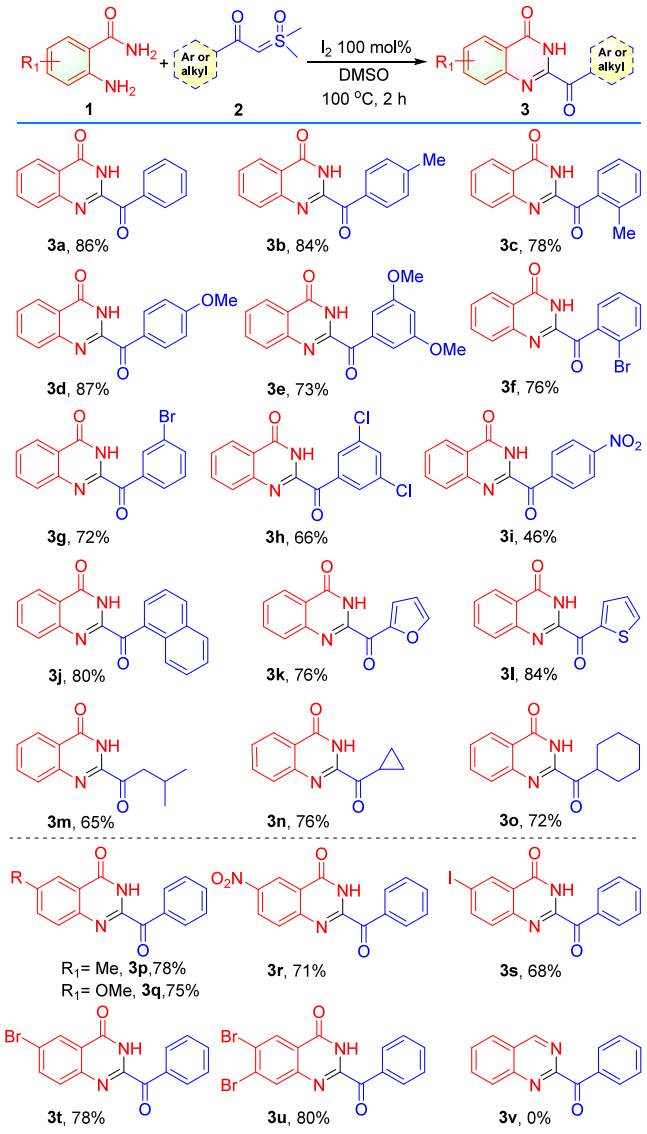
[a]General conditions: 2-Aminobenzamide **1a** (0.5 mmol), β-ketosulfoxonium ylide **2a** (0.56 mmol), and I_2 (x mmol) in 2 mL of solvent under air, stirred at a specified temperature for a specified time, except otherwise noted. [b]Heating source (oil bath). [c]Isolated yield.

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

16). We also performed the experiments under neat conditions with 10 and 100 mol % iodine, and at 100 mol % iodine, we obtained product **3a** with a 40% yield and product **4a** in a trace amount (Table 1, entries 18 and 19). After a thorough optimization process, the optimal reaction conditions were eventually attained, yielding high purity and yields for both 2-benzoyl quinazolinone **3a** and 2-phenyl quinazolinone **4a** (entries 4 and 16, respectively).

Under the optimized reaction conditions, we explored the generality and scope of the oxidative condensation reactions, as depicted in Scheme 2. Initially, we examined 2-amino-

Scheme 2. Substrate Scope for 2-Benzoyl Quinazolinones[a]



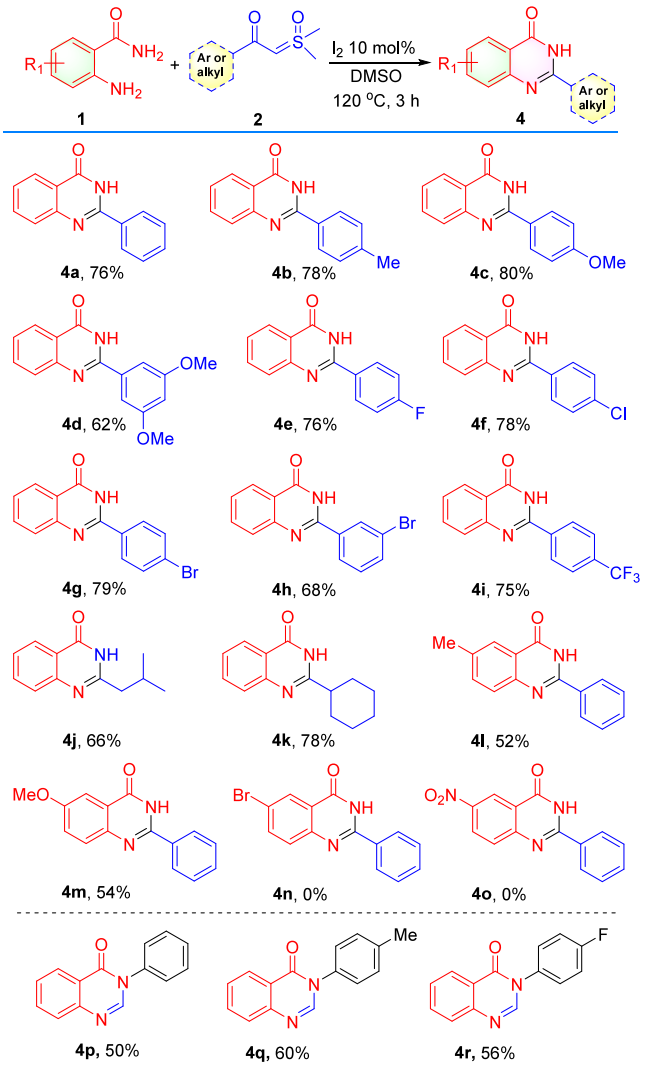
[a]Reaction conditions: 2-Aminobenzamides **1** (0.5 mmol), sulfoxonium ylides **2** (0.56 mmol), and I_2 (100 mol %) in 3 mL of DMSO solvent at 100 °C under air for 2 h. Yields are isolated yields.

benzamide **1a** in combination with a range of *β*-ketosulfoxonium ylides **2**, resulting in successful conversions into their respective quinazolinone derivatives **3** in good to high yields (entries **3a**−**3o**; 46−87%). Electron-rich sulfoxonium ylides **2**, featuring methyl and OMe substitutions at different positions on the aromatic ring, were effectively accommodated, resulting in high yields of the corresponding 2-benzoyl quinazolinone derivatives **3** (entries **3a**−**3e**; 73−87%). Similarly, sulfoxonium ylides **2** decorated with electron-withdrawing substituents, such as bromo, chloro, and nitro groups at different positions on the aromatic ring, were well tolerated and afforded the anticipated products in good yields (entries **3f**−**3i**, 46−76%). The optimized reaction conditions also promoted the compatibility of sulfoxonium ylides with naphthalene (**2j**) and heteroaryl (**2k** and **2l**) groups, leading to the synthesis of 2-benzoyl quinazolinones **3** with high yields (entries **3j**−**3l**; 76−84%). Moreover, under optimized conditions, a range of alkyl-substituted sulfoxonium ylides (**2m**−**2o**) were investigated, exhibiting favorable tolerance and yielding the respective products **3** in satisfactory yields (entries **3m**−**3o**; 65−76%). Additionally, to evaluate the versatility and applicability of the developed method, we examined a variety of substituted 2-aminobenzamides **1** in conjunction with sulfoxonium ylide **2a** utilizing the optimized reaction conditions. The 2-aminobenzamides **1** adorned with either electron-withdrawing or electron-donating groups were well accommodated, yielding the respective 2-benzoyl quinazolinone derivatives **3** in satisfactory yields (entries **3p**−**3u**; 68−80%).

Inspired by the aforementioned findings, we embarked on a comprehensive exploration to broaden the scope of synthesizing 2-aryl quinazolinones **4** from 2-aminobenzamides **1** and *β*-ketosulfoxonium ylides **2** in the presence of iodine (10 mol %), as depicted in Scheme 3. A diverse set of *β*-ketosulfoxonium ylides **2**, featuring either electron-donating or electron-withdrawing groups, was examined with 2-aminobenzamide **1a**, yielding the expected 2-aryl quinazolinones **4** in moderate to high yields (entries **4a**−**4i**; 62−80%). Similarly, a few aliphatic ylides (**2j** and **2k**) were assessed and demonstrated good tolerance, providing the respective products with moderate yields (entries **4j** and **4k**; 66−78%). Adding to these findings, we studied the reaction between different 2-aminobenzamide derivatives **1** featuring electron-donating groups with sulfoxonium ylides **2a** under optimized conditions. This exploration displayed good tolerability and yielded the expected products with reasonably satisfactory yields (entries **4l**−**4o**; 52−54%). However, when 2-aminobenzamide derivatives adorned with electron-withdrawing groups like bromo and NO_2 were reacted under optimized conditions, they failed to afford the desired products, instead resulting in a multitude of products. Moreover, it was unexpectedly found that when 2-amino-*N*-phenylbenzamides, bearing either electron-donating or electron-withdrawing groups, were reacted with sulfoxonium ylide **2a** in the presence of 10% iodine under optimized conditions, the quinazolin-4(3*H*)-one derivatives were obtained with yields of 50%, 60%, and 56% for compounds **4p**, **4q**, and **4r**, respectively. To demonstrate the scalability and practical usefulness of the developed protocol, we carried out numerous applications, as displayed in Scheme 4. In these studies, under optimized conditions, reactions on a gram scale were performed with 2-aminobenzamide **1a** (1.0 g, 7.4 mmol) and sulfoxonium ylide **2a** (1.6 g, 8.1 mmol) in the presence of iodine at two different concentrations (1.8 g, 7.4 mmol, and 0.18 g, 0.74 mmol) in 10 mL of DMSO solvent, yielding the desired products **3a** and **4a** at 78% (1.44 g) and 70% (1.15 g) yields, respectively. Quinazolinone derivatives **3a** and **4a**, which have been synthesized, are valuable building blocks that can be used to synthesize a variety of molecules, for example, the reaction of 2-benzoyl quinazolinone **3a** with bromoaceto-

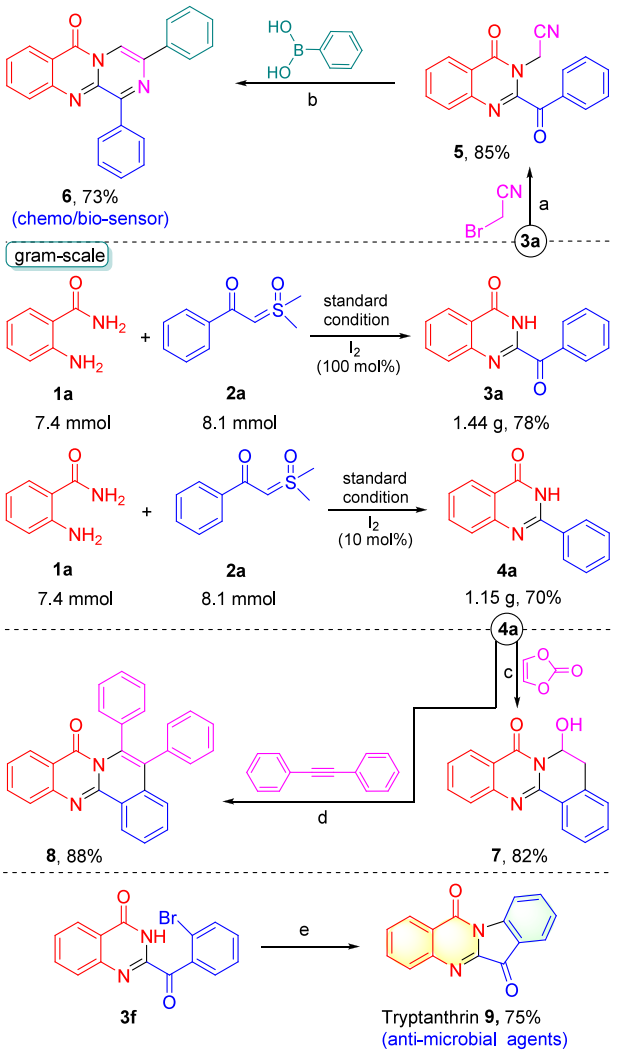
https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope for 2-Phenyl Quinazolinones[a]



[a]Reaction conditions: 2-Aminobenzamides **1** (0.5 mmol), *β*-ketosulfoxonium ylides **2** (0.56 mmol), and I_2 (10 mol %) in 2 mL of DMSO at 120 °C under air for 3 h. Yields are isolated yields.

Scheme 4. Synthetic Applications[a]



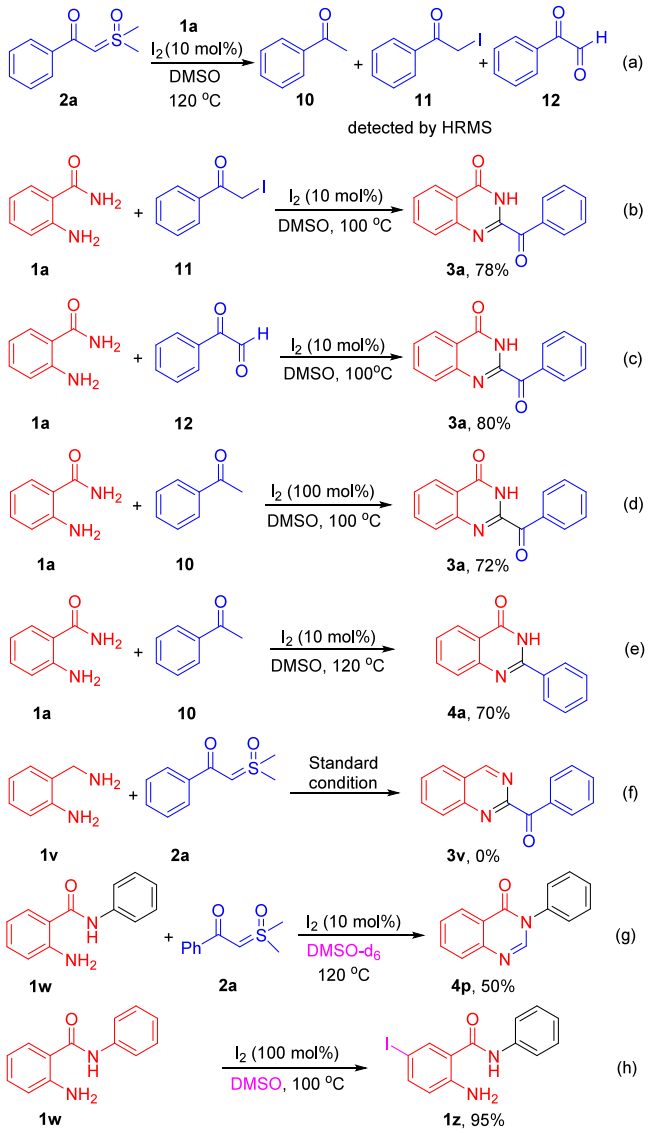
[a]Reagents and conditions: (a) Bromoacetonitrile, DIPEA, DMF, 70 °C, 12 h, 85%; (b) phenylboronic acid, $Pd(TFA)_2$ (5.0 mol %), bpy (10 mol %), CH_3SO_3H, H_2O, 100 °C, 24 h, 73%; (c) vinylene carbonate, $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), NaOAc, $AgSbF_6$, DCE, Ar atmosphere, 70 °C 12 h, 82%; (d) diphenylacetylene, $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OAc)_2$, Na_2CO_3, toluene, 90 °C, 16 h, 88%;. e) CuBr, K_2CO_3, DMSO, 100 °C, 40 min, 73%.

nitrile, facilitated by a base, in the formation of the quinazolinone intermediate **5** with an 85% yield. Subsequent treatment of this intermediate **5** with phenylboronic acid, catalyzed by palladium, generated the 1,3-pyrazino-fused quinazolinone **6** with 73% yield, which has fascinating chemo/biosensor properties.[12] Additionally, we conducted the Ru-catalyzed C−C/C−N coupling of 2-phenyl quinazolinones **4a** with vinylene carbonate[13] and diphenylacetylene,[14] resulting in the formation of fused quinazolinone **7** and polycyclic heteroarene **8** with yields of 82% and 88%, respectively. Fused polycyclic heteroaromatic structures, characterized by one or more nitrogen atoms, have garnered considerable interest due to their distinctive biological and photoelectrochemical properties.[13,14] Furthermore, tryptanthrin **9**, a natural alkaloid known for its antimicrobial and antitumor properties, was synthesized from the 2-benzoylquinazolinone **3f** using CuBr as a catalyst.[15]

To shed light on the reaction mechanism, we conducted a series of control experiments, as illustrated in Scheme 5. The 2-aminobenzamide **1a** and sulfoxonium ylide **2a** were treated with iodine in DMSO solvent under optimized conditions. The crude reaction mixture was analyzed using HRMS data after 30 min (see ESI, Figures S1 and S9). This analysis revealed the formation of acetophenone **10**, *α*-iodo acetophenone **11**, and phenylglyoxal **12** intermediates along with anticipated products (Scheme 5a). These findings suggest that the sulfoxonium ylide **2a** first transforms into *α*-iodoacetophenone **11**, which then converts to intermediates of acetophenone **10** (in the presence of catalytic iodine[16a] with HI liberating during the process[16b]) or phenylglyoxal (via Kornblum oxidation),[17] depending on the usage of I_2 mol % and temperature. Interestingly, a mass of m/z 146 corresponding to byproduct quinazolin-4(3*H*)-one was also detected. This finding strongly indicates that formaldehyde (HCHO) is formed in situ, which eventually leads to the generation of quinazolin-4(3*H*)-one as a minor byproduct (see ESI, Figures S1 and S9).[18] Treatment of *α*-iodoacetophenone **11** with 2-aminobenzamide **1a** resulted in the formation of product **3a**. Similarly, reacting phenylglyoxal

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 5. Control Experiments



12 with 2-aminobenzamide **1a** smoothly led to the generation of product **3a** as a major product. The outcomes of these two experiments suggest that the synthesis of the target product **4a** does not proceed through α-iodoacetophenone **11** and phenylglyoxal **12** as intermediates. When intermediates **11** and/or **12** are generated, product **3a** forms preferentially, essentially ruling out the chance of producing product **4a**. Additionally, we performed the reaction between 2-aminobenzylamine **1v** and sulfoxonium ylide **2a** under optimized conditions to assess the formation of a quinazoline derivative. Despite the complete consumption of ylide **2a**, the desired product **3v** was not obtained. The 2-aminobenzylamine **1v** remained unchanged, and a multitude of byproducts were generated. To determine the source of carbon in the formation of quinazolin-4(3*H*)-one and whether it originates from sulfoxonium ylide **2a** or DMSO,[19] we conducted a cross-experiment using DMSO-d_6. The results showed that the carbon from DMSO-d_6 was not incorporated into the product **4p**. This suggests that, in the presence of 10% iodine, the in-situ-generated formaldehyde acts as the one-carbon synthon (Scheme 5g). Further, when 2-amino-*N*-phenylbenzamide **1w** reacted with ylide **2a** in the presence of 100 mol % iodine, we did not observe the anticipated products. Instead, the reaction yielded multiple byproducts with the minor product being the iodinated 2-amino-*N*-phenylbenzamide **1z** and a trace amount of product **4p** (Scheme 5g and 5h). Additionally, when 2-amino-*N*-phenylbenzamide **1w** reacted with 100 mol % iodine in the absence of ylide **2a** in DMSO for 2 h, the iodination product 2-amino-5-iodo-*N*-phenylbenzamide, **1z**, was obtained with a 95% yield (Scheme 5h).

As a result, we suggested a possible reaction mechanism for the synthesis of **3a** and **4a** from **1a** and **2a**, as shown in Scheme 6. Initially, the α-carbon of β-ketosulfoxonium ylide **1** initiates a nucleophilic reaction with electrophilic iodine, generating intermediate **I**. Subsequently, the elimination of the highly acidic α-carbon proton generates intermediate **11**, which then releases DMSO and HI. In-situ-generated HI or I_2 promotes the reductive deiodination of α-iodoketone **11**, which generates intermediate **10**.[16a,b] The Lewis acid I_2 activates the intermediate acetophenone **10**, which then reacts with 2-aminobenzamide **1a** to form Schiff's base **II**, which is then cyclized to yield intermediate **III** (Scheme 6, path a). Intermediate **III** is iodinated to yield intermediate **IV**, which is subsequently coupled with DMSO to form the intermediate **V**. Finally, the elimination of formaldehyde and dimethyl sulfide from intermediate **V**, followed by oxidation, results in the formation of compound **4a**. In the synthesis pathway b for the synthesis of 2-benzoyl quinazolinone **3a**, the intermediate α-iodoacetophenone **11** transforms into phenylglyoxal **12** via Kornblum oxidation,[17] facilitated by DMSO. Excess or regenerated Lewis acid I_2 activates the aldehyde group of intermediate phenylglyoxal **12**.[20] Following this, 2-aminobenzamide **1a** reacts with phenylglyoxal **12** to form Schiff's base **VI**, which subsequently cyclizes to produce intermediate **VII**. Finally, it is proposed that intermediate **VII** was oxidized and aromatized in the presence of iodine to generate the desired product **3a**.[21]

CONCLUSION

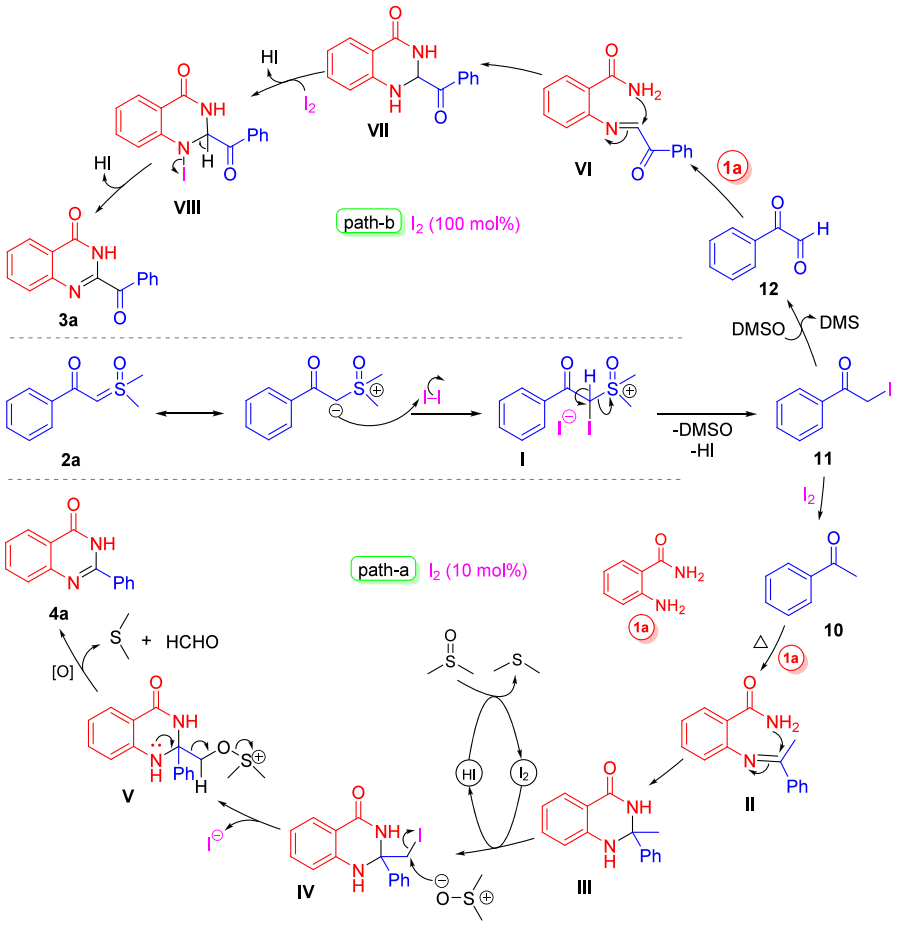
In conclusion, our research has led to the development of a new I_2-mediated, chemoselective process for synthesizing 2-benzoyl quinazolinones and 2-aryl/alkyl quinazolinones starting from sulfoxonium ylides. This method offers a simplified, metal-free route to these versatile nitrogen-containing heterocycles. The versatility, scalability, and practical applicability of this method were demonstrated through various applications, including reactions on a gram scale and the synthesis of biologically significant molecules such as tryptanthrin and the chemo/biosensor compound. The exploration of the mechanism shed light on the reaction pathways, revealing the novel behavior of sulfoxonium ylides and mapping out two unique pathways that lead to the synthesis of quinazolinones. This method marks a substantial progress in the synthesis of quinazolinones, showing great potential for use in drug discovery and development.

EXPERIMENTAL SECTION

General Method for the Preparation of Compound, 3. A mixture containing 2-aminobenzamide **1** (70 mg, 0.50 mmol) and β-ketosulfoxonium ylide **2** (111 mg, 0.56 mmol, 1.1 equiv) was stirred in 3 mL of DMSO. Iodine (130 mg, 0.50 mmol, 1.0 equiv) was then added, and the reaction was stirred under air at 100 °C for 2 h. The reaction progress was monitored by TLC. Upon completion, 20 mL of water was added followed by the gradual addition of a saturated $Na_2S_2O_3$ solution until the brown color faded. The reaction mixture

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 6. Plausible Reaction Mechanism



was extracted with EtOAc (3 × 10 mL). The organic layers were then mixed, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 8:2) to yield the desired product **3** in good to high yields.

2-Benzoylquinazolin-4(3H)-one, ***3a.***[21] White solid (107 mg, 86%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 185−186 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 10.46 (s, 1H), 8.49 (d, J = 7.8 Hz, 2H), 8.39 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 7.68−7.60 (m, 2H), 7.53 (t, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ (ppm) 185.7, 161.1, 147.6, 146.1, 134.9, 134.4, 134.1, 131.9, 129.6, 129.5, 128.5, 127.0, 123.3.

2-(4-Methylbenzoyl)quinazolin-4(3H)-one, ***3b.***[21] White solid (110 mg, 84%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 215−217 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.23 (s, 1H), 8.45 (d, J = 7.7 Hz, 2H), 8.40 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 185.0, 160.9, 147.6, 146.1, 145.6, 134.8, 132.0, 131.4, 129.4, 129.3, 129.2, 126.9, 123.3, 21.9.

2-(2-Methylbenzoyl)quinazolin-4(3H)-one, ***3c.***[13] White solid (103 mg, 78%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 218−220 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.69 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ (ppm) 190.7, 161.5, 149.9, 147.7, 139.1, 135.2, 134.9, 132.8, 132.1, 131.8, 129.1,128.9, 126.5, 125.9, 123.3, 20.7.

2-(4-Methoxybenzoyl)quinazolin-4(3H)-one, ***3d.***[21] White solid (122 mg, 87%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 185−187 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.62 (s, 1H), 8.22−8.19 (m, 3H), 7.89 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ (ppm) 185.8, 164.7, 161.5, 150.0, 147.7, 135.2, 133.9, 128.8, 128.7, 127.1, 126.5, 123.2, 114.5, 56.2.

2-(3,5-Dimethoxybenzoyl)quinazolin-4(3H)-one, ***3e.*** White solid (113 mg, 73%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 190−192 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.63 (s, 1H), 8.21 (d, J = 7.3 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.74 (s, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ (ppm) 185.7, 161.6, 154.9, 150.1, 149.1, 147.7, 135.2, 128.8, 128.7, 127.4, 127.0, 126.5, 123.2, 112.7, 111.4, 56.4, 56.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{15}N_2O_4^+$ 311.1026, found 311.1024.

2-(2-Bromobenzoyl)quinazolin-4(3H)-one, ***3f.***[12] White solid (125 mg, 76%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 205−207 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.88 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.87−7.83 (m, 1H), 7.79−7.71 (m, 2H), 7.70−7.63 (m, 2H), 7.59−7.52 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ (ppm) 190.0, 161.5, 148.4, 147.6, 138.1, 135.3, 133.5, 133.4, 131.6, 129.7, 129.1, 128.0, 126.6, 123.5, 120.3.

2-(3-Bromobenzoyl)quinazolin-4(3H)-one, ***3g.***[4d] White solid (118 mg, 72%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 212−214 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.22 (s, 1H), 8.69 (s, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.40 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.87 (t, J = 7.6 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.67

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

(t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 184.3, 160.7, 147.4, 145.5, 137.1, 135.6, 135.0, 134.6, 130.4, 130.0, 129.8, 129.5, 127.0, 123.3, 122.5.

2-(3,5-Dichlorobenzoyl)quinazolin-4(3H)-one, ***3h.*** White solid (104 mg, 66%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 250−252 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.87 (s, 1H), 8.22 (dd, J = 7.9, 1.1 Hz, 1H), 7.87−7.84 (m, 2H), 7.82 (d, J = 1.9 Hz, 1H), 7.71−7.62 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 188.2, 161.4, 148.4, 147.5, 137.4, 135.3, 134.8, 133.1, 133.0, 130.1, 130.0, 129.1, 128.0, 127.0, 124.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_9Cl_2N_2O_2^+$ 319.0036, found 319.0035.

2-(4-Nitrobenzoyl)quinazolin-4(3H)-one, ***3i.***[21] Gray solid (67 mg, 46%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 290−292 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.68 (s, 1H), 8.41−8.28 (m, 4H), 8.18 (d, J = 7.8 Hz, 1H), 7.86−7.82 (m, J 1H), 7.74−7.72 (m, 1H), 7.63 (t, J = 7.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 186.1, 161.0, 150.1, 148.0, 146.9, 139.5, 134.8, 132.3, 129.3, 128.6, 126.1, 123.7, 123.3.

2-(1-Naphthoyl)quinazolin-4(3H)-one, ***3j.***[21] White solid (120 mg, 80%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 215−217 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.43 (s, 1H), 8.41 (d, J = 8.1 Hz, 2H), 8.31 (d, J = 7.1 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.82 (s, 2H), 7.67−7.54 (m, 4H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 188.3, 161.1, 147.6, 146.6, 135.0, 134.1, 133.9, 132.7, 131.4, 130.5, 129.5, 128.7, 128.3, 127.0, 126.7, 125.2, 124.0, 123.2.

2-(Furan-2-carbonyl)quinazolin-4(3H)-one, ***3k.***[21] White solid (91 mg, 76%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 242−244 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.50 (s, 1H), 8.24−8.19 (m, 3H), 7.92 (d, J = 3.9 Hz, 2H), 7.67−7.65 (m, 1H), 6.88−6.86 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 173.0, 161.3, 151.0, 149.7, 148.0, 147.6, 135.3, 129.3, 129.1, 126.5, 123.6, 113.8.

2-(Thiophene-2-carbonyl)quinazolin-4(3H)-one, ***3l.***[21] White solid (107 mg, 84%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 213-215 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.53 (s, 1H), 8.43 (d, J = 3.6 Hz, 1H), 8.23−8.20 (m, 2H), 7.94−7.89 (m, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.34−7.32 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 177.8, 161.3, 148.1, 147.3, 139.7, 138.4, 138.2, 135.3, 129.4, 129.0, 128.9, 126.6, 123.6.

2-(4-Methylpentanoyl)quinazolin-4(3H)-one, ***3m.*** White solid (75 mg, 65%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 152−154 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.99 (s, 1H), 8.35 (d, J = 7.7 Hz, 1H), 7.88−7.82 (m, 2H), 7.61 (t, J = 7.3 Hz, 1H), 3.11 (s, 2H), 2.36−2.31 (m, 1H), 1.03 (d, J = 5.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 196.1, 160.7, 147.8, 145.3, 134.8, 129.3, 129.1, 127.0, 123.6, 44.8, 25.0, 22.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{15}N_2O_2^+$ 231.1128, found 231.1125.

2-(Cyclopropanecarbonyl)quinazolin-4(3H)-one, ***3n.***[22c] White solid (81 mg, 76%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 163−165 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.97 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 3.54−3.39 (m, 1H), 1.29 (s, 2H), 1.22−1.17 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 195.6, 160.6, 147.8, 145.4, 134.8, 129.2, 129.1, 126.9, 123.4, 15.3, 14.4.

2-(Cyclohexanecarbonyl)quinazolin-4(3H)-one, ***3o.*** White solid (92 mg, 72%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 170−172 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.01 (s, 1H), 8.36 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 3.84 (s, 1H), 1.98 (d, J = 6.9 Hz, 2H), 1.86 (d, J = 2.8 Hz, 2H), 1.76 (d, J = 8.4 Hz, 1H), 1.52−1.41 (m, 4H), 1.32−1.25 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 199.2, 160.9, 147.8, 144.5, 134.8, 129.3, 129.2, 126.9, 123.6, 43.1, 28.9, 25.8, 25.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2^+$ 257.1285, found 257.1280.

2-Benzoyl-6-methylquinazolin-4(3H)-one, ***3p.***[21] White solid (102 mg, 78%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 210−212 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.32 (s, 1H), 8.51 (d, J = 7.4 Hz, 2H), 8.20 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 6.5 Hz, 2H), 7.54 (t, J = 7.0 Hz, 2H), 2.54 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 185.6, 161.0, 145.5, 145.3, 140.3, 136.3, 134.2, 134.1, 131.8, 129.3, 128.4, 126.5, 123.0, 21.6.

2-Benzoyl-6-methoxyquinazolin-4(3H)-one, ***3q.***[4a] White solid (105 mg, 75%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 202−204 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.22 (s, 1H), 8.51 (d, J = 7.7 Hz, 2H), 7.86 (d, J = 8.9 Hz, 1H), 7.76 (s, 1H), 7.68 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 7.3 Hz, 2H), 7.43 (d, J = 8.9 Hz, 1H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 185.5, 160.7, 160.6, 144.1, 141.9, 134.1, 131.8, 131.1, 128.4, 125.0, 124.6, 106.6, 56.1.

2-Benzoyl-6-nitroquinazolin-4(3H)-one, ***3r.***[21] White solid (104 mg, 71%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 250−252 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 13.23 (s, 1H), 8.86 (s, 1H), 8.59 (d, J = 8.9 Hz, 2H), 8.17 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.77 (t, J = 7.4 Hz, 1H), 7.61 (t, J = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 187.4, 161.0, 152.6, 151.9, 146.5, 135.2, 134.1, 131.4, 130.5, 129.2, 129.0, 123.7, 122.3.

2-Benzoyl-6-iodoquinazolin-4(3H)-one, ***3s.***[21] White solid (128 mg, 68%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 235−237 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.33 (s, 1H), 8.74 (d, J = 1.8 Hz, 1H), 8.50 (d, J = 7.8 Hz, 2H), 8.13 (dd, J = 8.5, 1.9 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 185.3, 159.4, 146.8, 146.3, 143.8, 135.9, 134.5, 133.8, 131.8, 130.9, 128.5, 124.7, 95.0.

2-Benzoyl-6-bromoquinazolin-4(3H)-one, ***3t.***[4a] Yellow solid (128 mg, 78%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 246−248 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.88 (s, 1H), 8.28 (s, 1H), 8.16 (d, J = 7.3 Hz, 2H), 8.02 (d, J = 8.6 Hz, 1H), 7.79−7.71 (m, 2H), 7.59 (t, J = 7.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 187.4, 160.5, 149.9, 146.6, 138.0, 134.8, 134.4, 131.3, 131.1, 129.1, 128.7, 125.0, 121.7.

2-Benzoyl-6,7-dibromoquinazolin-4(3H)-one, ***3u.*** Yellow solid (162 mg, 80%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 263−265 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 13.05 (s, 1H), 8.45 (d, J = 2.1 Hz, 1H), 8.32 (d, J = 7.4 Hz, 2H), 8.27 (d, J = 2.1 Hz, 1H), 7.76 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 186.5, 160.3, 150.0, 144.8, 140.4, 134.9, 134.3, 131.7, 129.0, 128.5, 126.2, 125.0, 121.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_9Br_2N_2O_2^+$ 406.9025, found 406.9032.

General Method for the Preparation of Compound, 4. A mixture of 2-aminobenzamide **1** (70 mg, 0.50 mmol) and β-ketosulfoxonium ylide **2** (111 mg, 0.56 mmol, 1.1 equiv) in 2 mL of DMSO was stirred followed by the addition of iodine (13 mg, 0.05 mmol, 0.1 equiv). The reaction was then stirred under air at 120 °C for 3 h. TLC monitored progress, and upon completion, 20 mL of water was added to the mixture. A saturated aq. $Na_2S_2O_3$ solution was gradually added until the brown color dissipated. The mixture was then extracted with EtOAc (3 × 10 mL), and the organic layers were mixed and dried over Na_2SO_4. The solvent was removed under reduced pressure using a rotary evaporator to obtain the crude product. This crude product was then purified by column chromatography on silica gel using a mixture of petroleum ether/EtOAc (8:2) as the eluent, isolating the anticipated product **4** in moderate to good yields.

2-Phenylquinazolin-4(3H)-one, ***4a.***[22b] White solid (84 mg, 76%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 240−242 °C; ^1H NMR (500 MHz,

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

$CDCl_3$) δ (ppm) 11.81 (s, 1H), 8.32−8.26 (m, 3H), 7.85−7.78 (m, 2H), 7.58−7.57 (m, 3H), 7.50 (t, J = 7.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ (ppm) 164.0, 151.9, 149.5, 135.0, 132.8, 131.8, 129.1, 128.0, 127.6, 126.9, 126.4, 120.9.

2-(p-Tolyl)quinazolin-4(3H)-one, ***4b***.[22b] White solid (92 mg, 78%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 248−250 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.47 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 7.9 Hz, 2H), 7.83 (t, J = 7.6 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 162.7, 152.7, 149.3, 141.9, 135.0, 130.4, 129.7, 128.2, 127.9, 126.9, 126.3, 121.4, 21.5.

2-(4-Methoxyphenyl)quinazolin-4(3H)-one, ***4c***.[22b] White solid (100 mg, 80%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 252−254 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.41 (s, 1H), 8.20 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 7.8 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 162.8, 162.3, 152.3, 149.4, 135.0, 129.9, 127.8, 126.6, 126.3, 125.3, 121.2, 114.5, 55.9.

2-(3,5-Dimethoxyphenyl)quinazolin-4(3H)-one, ***4d***.[22d] White solid (87 mg, 62%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/3); mp 263−265 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.44 (s, 1H), 8.14 (d, J = 7.3 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.82 (s, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 6.6 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 162.8, 152.3, 152.0, 149.4, 149.0, 135.0, 127.8, 126.6, 126.3, 125.2, 121.6, 121.2, 111.8, 111.1, 56.1.

2-(4-Fluorophenyl)quinazolin-4(3H)-one, ***4e***.[22b] White solid (91 mg, 76%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 250−254 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.58 (s, 1H), 8.27−8.25 (m, 2H), 8.16 (d, J = 7.8 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 8.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 165.3, 163.7, 162.7, 151.9, 149.1, 135.1, 130.9 (d, J = 9.2 Hz), 129.7 (d, J = 2.4 Hz), 127.9, 127.1, 126.3, 121.4, 116.2, 116.0. $^{19}F\{^1H\}$ NMR (565 MHz, DMSO-d_6) δ (ppm) −108.23.

2-(4-Chlorophenyl)quinazolin-4(3H)-one, ***4f***.[22b] White solid (99 mg, 78%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 290−292 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.61 (s, 1H), 8.21 (d, J = 7.6 Hz, 2H), 8.16 (d, J = 7.9 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 162.6, 151.8, 149.1, 136.8, 135.2, 132.0, 130.1, 129.2, 128.0, 127.3, 126.3, 121.5.

2-(4-Bromophenyl)quinazolin-4(3H)-one, ***4g***.[22b] White solid (118 mg, 79%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 299−301 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.60 (s, 1H), 8.15−8.11 (m, 3H), 7.84 (t, J = 7.6 Hz, 1H), 7.76−7.73 (m, 3H), 7.53 (t, J = 7.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 162.6, 151.9, 149.1, 135.2, 132.4, 132.1, 130.3, 128.0, 127.3, 126.4, 125.7, 121.5.

2-(3-Bromophenyl)quinazolin-4(3H)-one, ***4h***.[22b] White solid (101 mg, 68%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 288−290 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.63 (s, 1H), 8.39 (s, 1H), 8.18 (dd, J = 17.2, 7.8 Hz, 2H), 7.86 (t, J = 7.6 Hz, 1H), 7.79 (dd, J = 15.0, 8.0 Hz, 2H), 7.60−7.49 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 162.1, 150.9, 148.5, 134.9, 134.7, 134.1, 130.8, 130.4, 127.6, 127.0, 126.8, 125.9, 121.9, 121.1.

2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3H)-one, ***4i***.[22b] White solid (108 mg, 75%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 301−303 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.74 (s, 1H), 8.37 (d, J = 7.9 Hz, 2H), 8.18 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 7.8 Hz, 2H), 7.86 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ (ppm) 162.6, 151.7, 148.9, 137.1, 135.2, 132.2, 131.7, 131.5, 129.2, 128.2, 127.6, 126.4, 125.9 (d, J = 3.8 Hz), 125.3, 123.5, 121.7. $^{19}F\{^1H\}$ NMR (565 MHz, DMSO-d_6) δ (ppm) −61.35.

2-Isopentylquinazolin-4(3H)-one, ***4j***. White solid (67 mg, 66%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 168−170 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 11.94 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 2.68 (d, J = 7.2 Hz, 2H), 2.38−2.30 (m, 1H), 1.07 (d, J = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 164.3, 164.2, 156.3, 156.2, 149.5, 134.8, 127.3, 126.4, 126.2, 120.5, 44.8, 28.0, 22.4. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_2O^+$ 203.1179, found 203.1181.

2-Cyclohexylquinazolin-4(3H)-one, ***4k***.[22a] White solid (88 mg, 78%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/5); mp 185−187 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 11.63 (s, 1H), 8.28 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.72 (t, J = 8.3 Hz, 1H), 7.47 (t, J = 7.3 Hz, 1H), 2.75−2.71 (m, 1H), 2.06 (d, J = 12.7 Hz, 2H), 1.93 (d, J = 12.4 Hz, 2H), 1.81−1.75 (m, 3H), 1.49−1.38 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 164.2, 160.2, 149.6, 134.7, 127.4, 126.3, 126.2, 120.8, 44.9, 30.5, 26.0, 25.7.

6-Methyl-2-phenylquinazolin-4(3H)-one, ***4l***.[22a] White solid (61 mg, 52%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 252−254 °C; ^1H NMR (500 MHz, DMSO-d_6) δ (ppm) 12.44 (s, 1H), 8.12 (d, J = 7.0 Hz, 2H), 7.91 (s, 1H), 7.80−7.49 (m, 5H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ (ppm) 162.6, 152.2, 146.9, 136.9, 136.4, 133.1, 131.8, 129.1, 128.2, 127.6, 125.8, 121.2, 21.4.

6-Methoxy-2-phenylquinazolin-4(3H)-one, ***4m***.[22a] White solid (68 mg, 54%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/4); mp 260−262 °C; ^1H NMR (500 MHz, DMSO-d_6) δ (ppm) 12.47 (s, 1H), 8.12 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 9.1 Hz, 1H), 7.54−7.48 (m, 4H), 7.41−7.39 (m, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ (ppm) 162.6, 158.3, 150.6, 143.7, 133.3, 131.6, 129.8, 129.1, 128.0, 124.6, 122.3, 106.4, 56.2.

3-Phenylquinazolin-4(3H)-one, ***4p***.[23] White solid (55 mg, 50%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 145−147 °C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.38 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 7.83−7.75 (m, 2H), 7.60−7.53 (m, 3H), 7.50 (t, J = 7.3 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ (ppm) 160.8, 148.0, 146.2, 137.6, 134.6, 129.7, 129.2, 127.71, 127.67, 127.3, 127.1, 122.5.

3-(p-Tolyl)quinazolin-4(3H)-one, ***4q***.[23] White solid (71 mg, 60%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 156−158 °C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.36 (d, J = 7.9 Hz, 1H), 8.11 (s, 1H), 7.81−7.73 (m, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.32 (dd, J = 19.9, 8.6 Hz, 4H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ (ppm) 160.9, 148.0, 146.4, 139.3, 135.0, 134.5, 130.3, 127.6, 127.2, 126.8, 122.5, 21.2.

3-(4-Fluorophenyl)quinazolin-4(3H)-one, ***4r***.[23] White solid (67 mg, 56%); purified by column chromatography (silica gel 100−200 mesh, ethyl acetate/hexane, v/v = 1/6); mp 170−172 °C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.36 (d, J = 8.0 Hz, 1H), 8.10 (s, 1H), 7.84−7.75 (m, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.42 (dd, J = 8.8, 5.0 Hz, 2H), 7.25 (dd, J = 14.8, 6.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ (ppm) 163.7, 161.7, 160.9, 147.9, 145.9, 134.8, 133.5, 128.99 (d, J = 8.5 Hz), 127.78 (d, J = 13.1 Hz), 127.2, 122.4, 116.8, 116.6.

Synthesis of 2-(2-Benzoyl-4-oxoquinazolin-3(4H)-yl) Acetonitrile, ***5***.[24a] A solution of 2-benzoylquinazolin-4(3*H*)-one **3a** (3 mmol), bromoacetonitrile (9 mmol), and DIPEA (7.5 mmol) in 3 mL of DMF was heated at 70 °C for 12 h. Upon completion of the reaction, confirmed by TLC, the mixture was quenched with water and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated.

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

The crude residue was then purified by silica gel column chromatography (100−200 mesh) using a solvent system of ethyl acetate/petroleum ether (1:3) to yield pure product **5** as a gray solid with an 85% yield (737 mg); mp 210−212 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.38 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 2H), 7.85 (t, J = 7.6 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 5.15 (s, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 187.3, 160.4, 147.8, 145.5, 135.5, 135.3, 133.8, 131.2, 129.5, 128.9, 128.6, 127.4, 121.3, 114.2, 31.3.

*Synthesis of 1,3-Diphenyl-6H-pyrazino[2,1-b]quinazolin-6-one, **6**.*[24a] To a 10 mL Schlenk tube, 2-(2-benzoyl-4-oxoquinazolin-3(4*H*)-yl) acetonitrile **5** (0.2 mmol) and phenylboronic acid (0.2 mmol) were combined with $Pd(TFA)_2$ (5 mol %), bpy (10 mol %), and MsOH (3 equiv) in 2 mL of H_2O. The mixture was heated at 100 °C for 24 h. Upon completion, the reaction was quenched with ice-cold saturated aqueous $NaHCO_3$. The resulting mixture was then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was then purified by silica gel column chromatography (100−200 mesh) using a solvent system of ethyl acetate/petroleum ether (1:3), yielding the pure product **6** as a yellow solid with a 73% yield (51 mg); mp 246−247 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.04 (s, 1H), 8.51 (d, J = 7.7 Hz, 1H), 8.48−8.37 (m, 2H), 8.13 (d, J = 7.6 Hz, 2H), 7.95−7.87 (m, 2H), 7.63−7.55 (m, 4H), 7.52 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 158.5, 158.3, 147.5, 139.2, 137.3, 136.5, 135.7, 135.2, 131.1, 130.7, 129.2, 129.1,128.8, 128.1, 127.4, 126.2, 117.58, 111.3.

*Synthesis of 6-Hydroxy-5,6-dihydro-8H-isoquinolino[1,2-b]-quinazolin-8-one, **7**.*[24b] A solution of 2-phenylquinazolin-4(3*H*)-one **4a** (0.2 mmol, 1.0 equiv), vinylene carbonate (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgSbF_6$ (20 mol %), and NaOAc (0.4 mmol) in 1 mL of DCE was stirred under an argon atmosphere in an oil bath at 80 °C for 12 h. Upon completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure. The crude residue was then purified by silica gel column chromatography (100−200 mesh) using a solvent system of ethyl acetate/petroleum ether (1:3), yielding pure product **7** as a white solid with an 82% yield (43 mg); mp 220−222 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 8.42 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.1 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.56−7.52 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 6.74 (d, J = 3.5 Hz, 1H), 6.68 (s, 1H), 3.36−3.31 (m, 1H), 3.18 (d, J = 15.4 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ (ppm) 160.7, 148.6, 147.8, 135.3, 135.2, 132.3, 129.5, 128.8, 127.9, 127.5, 127.4, 127.2, 127.0, 121.1, 71.6, 34.8.

*Synthesis of 5, 6-Diphenyl-8H-isoquinolino[1,2-b]quinazolin-8-one, **8**.*[24c] A solution of 2-phenylquinazolin-4(3*H*)-one **4a** (0.2 mmol, 1.0 equiv), diphenylacetylene (0.3 mmol, 1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Na_2CO_3 (0.4 mmol, 2.0 equiv), and $Cu(OAc)_2$ (0.4 mmol, 2.0 equiv) in 3 mL of toluene was added to a reaction tube. The mixture was stirred in an oil bath at 90 °C for 16 h. Afterward, it was diluted with CH_2Cl_2 and transferred to a round-bottom flask. Silica was added to the flask, and the volatiles were evaporated under reduced pressure. Purification was performed by flash column chromatography on silica gel (100−200 mesh) using a solvent system of ethyl acetate/petroleum ether (1:9), yielding pure product **8** as a white solid with an 88% yield (70 mg); mp 261−262 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.11 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.25 (dd, J = 12.5, 5.3 Hz, 3H), 7.18 (d, J = 8.0 Hz, 1H), 7.13−7.10 (m, 3H), 7.08 (d, J = 6.0 Hz, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 161.3, 147.5, 146.9, 137.0, 135.5, 135.2, 134.4, 133.9, 132.0, 131.2, 128.5, 128.3, 128.0, 127.8, 127.3, 127.2, 127.1, 126.9, 126.8, 126.2, 125.6, 120.3.

*Synthesis of Indolo[2,1-b]quinazoline-6,12-dione (Tryptanthrin), **9**.*[24d] A solution of 2-(3-bromobenzoyl)quinazolin-4(3*H*)-one **3f** (0.4 mmol), CuBr (0.08 mmol), and K_2CO_3 (1.6 mmol) in 2 mL of DMSO was stirred in an oil bath at 100 °C for 40 min. Upon completion of the reaction, as monitored by TLC, the mixture was quenched with an NH_4Cl solution and extracted with DCM. The combined organic layers were washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (100−200 mesh) using a solvent system of ethyl acetate/petroleum ether (1:3), yielding tryptanthrin **9** as a yellow solid with a 75% yield (74 mg); mp 272−274 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.60 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 7.7 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.84 (t, J = 7.4 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 182.6, 158.1, 146.6, 146.3, 144.3, 138.3, 135.1, 130.7, 130.2, 127.5, 127.2, 125.4, 123.7, 121.9, 118.0.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01354.

Experimental procedures, characterization information, and NMR spectra copies for compounds **1p−1u**, **1z**, **2a−2s**, **3a−3u**, **4a−4o**, and **5−9** (PDF)

FAIR data, including the primary NMR FID files, for compounds **1p−1u**, **1z**, **2a−2s**, **3a−3u**, **4a−4o**, and **5−9** (ZIP)

FAIR data, including the primary HRMS FID files, for compounds **1p−1u**, **1z**, **2a−2s**, **3a−3u**, **4a−4o**, and **5−9** (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Satyendra Kumar Pandey − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221 005, India*; orcid.org/0000-0001-7839-567X; Email: skpandey.chem@bhu.ac.in

Authors

Ajay Kant Gola − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221 005, India*

Naveen Kumar − *Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221 005, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.4c01354

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.K.P. expresses gratitude to SERB New Delhi for the CRG/2020/005562 project grant. A.K.G. sincerely thanks SERB New Delhi for the Senior Research Fellowship (SRF). N.K. acknowledges CSIR New Delhi for the SRF. The authors are grateful to the BHU IoE incentive grant and SATHI-BHU for NMR analysis.

■ REFERENCES

(1) (a) Gupta, T.; Rohilla, A.; Pathak, A.; Akhtar, J. M.; Haider, R. M.; Yar, S. M. Current Perspectives on Quinazolines with Potent Biological Activities. *Synth. Commun.* **2018**, *48*, 1099−1127. (b) Shreder, R. K.; Wong, S. M.; Nomanbhoy, T.; Leventhal, S. P.;

Fuller, R. S. Synthesis of AX7593, a Quinazoline-Derived Photoaffinity Probe for EGFR. *Org. Lett.* **2004**, *6*, 3715−3718.
(2) (a) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent Advances in the Structural Library of Functionalized Quinazoline and Quinazolinone Scaffolds: Synthetic Approaches and Multifarious Applications. *Eur. J. Med. Chem.* **2014**, *76*, 193−244. (b) Michael, J. P. Quinoline, Quinazoline and Acridone Alkaloids. *Nat. Prod. Rep.* **2008**, *25*, 166−187.
(3) (a) Anil, S. M.; Shobith, R.; Kiran, K. R.; Swaroop, T. R.; Mallesha, N.; Sadashiva, M. P. Facile Synthesis of 1,4-Benzodiazepine-2,5-diones and Quinazolinones from Amino Acids as Anti-Tubercular Agents. *New J. Chem.* **2019**, *43*, 182−187. (b) Chang, K.-M.; Chen, L.-C.; Tzeng, C.-C.; Lu, Y.-H.; Chen, I. L.; Juang, S.-H.; Wang, T.-C. Synthesis and Antiproliferative Evaluation of Oxime, Methyloxime, and Amide-Containing Quinazolinones. *J. Chin. Chem. Soc.* **2018**, *65*, 1110−1118. (c) Brown, C. E.; Kong, T.; McNulty, J.; D'Aiuto, L.; Williamson, K.; McClain, L.; Piazza, P.; Nimgaonkar, V. L. Discovery of Potent Antiviral (HSV-1) Quinazolinones and Initial Structure-Activity Relationship Studies. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4601−4605.
(4) (a) Jayaram, A.; Govindan, K.; Kannan, V. R.; Thavasianandam Seenivasan, V.; Chen, N.-Q.; Lin, W.-Y. Iodine-Promoted Oxidative Cyclization of Acylated and Alkylated Derivatives from Epoxides toward the Synthesis of Aza Heterocycles. *J. Org. Chem.* **2023**, *88*, 1749−1761. (b) Sahoo, S.; Pal, S. Copper-Catalyzed One-Pot Synthesis of Quinazolinones from 2-Nitrobenzaldehydes with Aldehydes: Application toward the Synthesis of Natural Products. *J. Org. Chem.* **2021**, *86*, 18067−18080. (c) Wang, K.; Chen, H.; Dai, X.; Huang, X.; Feng, Z. Palladium-Catalyzed One-Pot Synthesis of 2-Substituted Quinazolin-4(3*H*)-ones from *o*-Nitrobenzamide and Alcohols. *RSC Adv.* **2021**, *11*, 13119−13123. (d) Nguyen, T. B.; Hou, J.-Y.; Retailleau, P. Sulfur-Promoted Synthesis of 2-Aroylquinazolin-4(3*H*)-ones by Oxidative Condensation of Anthranilamide and Acetophenones. *Adv. Synth. Catal.* **2019**, *361*, 3337−3341. and references cited therein.
(5) (a) Dutta, B.; Dutta, N.; Dutta, A.; Gogoi, M.; Mehra, S.; Kumar, A.; Deori, K.; Sarma, D. [DDQM][HSO_4]/TBHP as a Multifunctional Catalyst for the Metal Free Tandem Oxidative Synthesis of 2-Phenylquinazolin-4(3*H*)-ones. *J. Org. Chem.* **2023**, *88*, 14748−14752. (b) Dutta, N.; Dutta, B.; Dutta, A.; Sarma, B.; Sarma, D. Room Temperature Ligand-Free Cu_2O−H_2O_2 Catalyzed Tandem Oxidative Synthesis of Quinazoline-4(3*H*)-one and Quinazoline Derivatives. *Org. Biomol. Chem.* **2023**, *21*, 748−753. (c) Das, S.; Mondal, R.; Chakraborty, G.; Guin, A. K.; Das, A.; Paul, N. D. Zinc Stabilized Azo-anion Radical in Dehydrogenative Synthesis of N-Heterocycles. An Exclusively Ligand Centered Redox Controlled Approach. *ACS Catal.* **2021**, *11*, 7498−7512. (d) Jang, Y.; Lee, B. S.; Hong, J.; Chun, S.; Lee, J.; Hong, S. Synthesis of 2-Aryl Quinazolinones via Iron-catalyzed Cross-dehydrogenative Coupling (CDC) between N−H and C−H bonds. *Org. Biomol. Chem.* **2020**, *18*, 5435−5441. (e) Samim, S. A.; Roy, B. C.; Nayak, S.; Kundu, S. Cobalt Catalyzed Tandem Transformation of 2-Aminobenzonitriles to Quinazolinones Using Hydration and Dehydrogenative Coupling Strategy. *J. Org. Chem.* **2020**, *85*, 11359−11367. (f) Das, S.; Sinha, S.; Samanta, D.; Mondal, R.; Chakraborty, G.; Brandao, P.; Paul, D. N. Metal−Ligand Cooperative Approach to Achieve Dehydrogenative Functionalization of Alcohols to Quinolines and Quinazolin-4(3*H*)-ones under Mild Aerobic Conditions. *J. Org. Chem.* **2019**, *84*, 10160. (g) Hu, Y.; Li, S.; Li, H.; Li, Y.; Li, J.; Duanmu, C.; Li, B. Copper Catalyzed Tandem Oxidative Synthesis of Quinazolinones from 2-Aminobenzonitriles and Benzyl Alcohols. *Org. Chem. Front.* **2019**, *6*, 2744−2748. and references cited therein.
(6) (a) Chai, H.; Li, J.; Yang, L.; Lu, H.; Qi, Z.; Shi, D. Copper-Catalyzed Tandem N-Arylation/Condensation: Synthesis of Quinazolin-4(3H)-ones from 2-Halobenzonitriles and Amides. *RSC Adv.* **2014**, *4*, 44811−44814. (b) Cheng, R.; Guo, T.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. One-Pot Synthesis of Quinazolinones from Anthranilamides and Aldehydes *via p*-Toluenesulfonic Acid Catalyzed Cyclocondensation and Phenyliodine Diacetate Mediated Oxidative Dehydrogenation. *Synthesis* **2013**, *45*, 2998−3006. (c) Balakumar, C.; Lamba, P.; Pran Kishore, D.; Lakshmi Narayana, B.; Venkat Rao, K.; Rajwinder, K.; Raghuram Rao, A.; Shireesha, B.; Narsaiah, B. Synthesis, Anti-Inflammatory Evaluation and Docking Studies of Some New Fluorinated Fused Quinazolines. *Eur. J. Med. Chem.* **2010**, *45*, 4904−4913. (d) Mitobe, Y.; Ito, S.; Mizutani, T.; Nagase, T.; Sato, N.; Tokita, S. Development of a Selective and Potent Radioactive Ligand for Histamine H(3) receptors: A Compound Potentially useful for Receptor Occupancy Studies. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4075−4078. (e) Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. A. A Novel Method for the Synthesis of 4(3*H*)-Quinazolinones. *Tetrahedron Lett.* **2004**, *45*, 3475−3476.
(7) Hu, B.-Q.; Wang, L.-X.; Yang, L.; Xiang, J.-F.; Tang, Y.-L. Copper-Catalyzed Intramolecular C−C Bond Cleavage to Construct 2-Substituted Quinazolinones. *Eur. J. Org. Chem.* **2015**, *2015*, 4504−4509.
(8) Patel, M. S.; Chada, H.; Biswal, S.; Sharma, S.; Sharada, S. D. Copper-Catalyzed Intramolecular α-C−H Amination via Ring-Opening Cyclization Strategy to Quinazolin-4-ones: Development and Application in Rutaecarpine Synthesis. *Synthesis* **2019**, *51*, 3160−3170.
(9) For selected examples, see: (a) Prabhakar Ganesh, P. S. K.; Muthuraja, P.; Gopinath, P. Rh(III) Catalyzed Redox-Neutral C−H Activation/[5 + 2] Annulation of Aroyl Hydrazides and Sulfoxonium Ylides: Synthesis of Benzodiazepinones. *Org. Lett.* **2023**, *25*, 8361−8366. (b) Yang, Q.; Bai, J.; Yang, H.; Yao, Y.; Yao, Y.; Sun, J.; Sun, S. [Cp*$IrCl_2$]$_2$ Catalyzed Amidocarbonation of Olefins with Sulfoxonium Ylides toward Functionalized Isoindolin-1-ones. *Org. Lett.* **2023**, *25*, 7148−7153. (c) Jiang, H.; Zhang, H.; Xiong, W.; Qi, C.; Wu, W.; Wang, L.; Cheng, R. Iridium-Catalyzed Three Component Coupling Reaction of Carbon Dioxide, Amines, and Sulfoxonium Ylides. *Org. Lett.* **2019**, *21*, 1125−1129. (d) Li, C.; Li, M.; Zhong, W.; Jin, Y.; Li, J.; Wu, W.; Jiang, H. Palladium-Catalyzed Oxidative Allylation of Sulfoxonium Ylides: Regioselective Synthesis of Conjugated Dienones. *Org. Lett.* **2019**, *21*, 872−875. (e) Vaitla, J.; Bayer, A. Sulfoxonium Ylide Derived Metal Carbenoids in Organic Synthesis. *Synthesis* **2019**, *51*, 612−628. (f) Talero, A. G.; Martins, B. S.; Burtoloso, A. C. B. Coupling of Sulfoxonium Ylides with Arynes: A Direct Synthesis of Pro-Chiral Aryl Ketosulfoxonium Ylides and its Application in the Preparation of α-Aryl Ketones. *Org. Lett.* **2018**, *20*, 7206−7211. (g) Vaitla, J.; Bayer, A.; Hopmann, K. H. Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4277−4281; *Angew. Chem.* **2017**, *129*, 4341−4345. (h) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. Sulfoxonium and Sulfonium Ylides as Diazocarbonyl Equivalents in Metal-Catalyzed Insertion Reactions. *Eur. J. Org. Chem.* **2013**, *2013*, 5005−5016.
(10) For recent reviews, see: (a) Bhorali, P.; Sultana, S.; Gogoi, S. Recent Advances in Metal-Catalyzed C−H Bond Functionalization Reactions of Sulfoxonium Ylides. *Asian J. Org. Chem.* **2022**, *11*, e202100754. (b) Kumar, A.; Sherikar, M. S.; Hanchate, V.; Prabhu, K. R. Application of Sulfoxonium Ylide in Transition-Metal-Catalyzed C−H Bond Activation and Functionalization Reactions. *Tetrahedron* **2021**, *101*, 132478. (c) Kumar, S.; Nunewar, S.; Oluguttula, S.; Nanduri, S.; Kanchupalli, V. Recent Advances in Rh(III)/Ir(III)-Catalyzed C−H Functionalization/Annulation *via* Carbene Migratory Insertion. *Org. Biomol. Chem.* **2021**, *19*, 1438−1458.
(11) (a) Saini, R. K.; Borpatra, P. J.; Chaubey, T. N.; Pandey, S. K. I_2 Mediated Site-Selective C-H Functionalization: Access to *p*-Amino-Substituted Unsymmetrical Benzils and Quinoxalines from Sulfoxonium Ylides. *J. Org. Chem.* **2024**, *89*, 5536−5545. (b) Gola, A. K.; Sharma, A.; Pandey, S. K. Synthesis of α-Carbonyl-α'-amide Sulfoxonium Ylides from Isocyanates with Complete Atom Economy. *Org. Lett.* **2023**, *25*, 1214−1217. (c) Sharma, A.; Gola, A. K.; Pandey, S. K. Straightforward Access to α-Thiocyanoketones and Thiazoles from Sulfoxonium Ylides. *Chem. Commun.* **2023**, *59*, 10247−10250. (d) Chaubey, T. N.; Borpatra, P. J.; Sharma, A.; Pandey, S. K. Metal-free Syntheses of α-Ketothioamide and α-Ketoamide Derivatives from Sulfoxonium Ylides. *Org. Lett.* **2022**, *24*, 8062−8066.

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX

(12) Zhang, Y.; Xiong, W.; Chen, L.; Shao, Y.; Li, R.; Chen, Z.; Ge, J.; Lv, N.; Chen, J. Palladium-Catalyzed Cascade Reactions in Aqueous Media: Synthesis and Photophysical Properties of Pyrazino-Fused Quinazolinones. *Org. Chem. Front.* **2021**, *8*, 304−309.
(13) Wang, Z.-H.; Wang, H.; Wang, H.; Li, L.; Zhou, M.-D. Ruthenium(II)-Catalyzed C−C/C−N Coupling of 2-Arylquinazolinones with Vinylene Carbonate: Access to Fused Quinazolinones. *Org. Lett.* **2021**, *23*, 995−999.
(14) Lu, H.; Yang, Q.; Zhou, Y.; Guo, Y.; Deng, Z.; Ding, Q.; Peng, Y. Cross-Coupling/Annulations of Quinazolones with Alkynes for Access to Fused Polycyclic Heteroarenes under Mild Conditions. *Org. Biomol. Chem.* **2014**, *12* (15), 758−764.
(15) Guo, H.; Zhai, J.; Fan, X. An I_2-Mediated Cascade Reaction of 2′-Bromoacetophenones with Benzohydrazides/Benzamides Leading to Quinazolino[3,2-*b*]cinnoline or Tryptanthrin Derivatives. *Org. Biomol. Chem.* **2017**, *15*, 1521−1529.
(16) (a) Nobuta, T.; Hirashima, S.-C.; Tada, N.; Miura, T.; Itoh, A. One-Pot Metal-Free Syntheses of Acetophenones from Styrenes through Aerobic Photo-oxidation and Deiodination with Iodine. *Org. Lett.* **2011**, *13*, 2576−2579. (b) Penso, M.; Mottadelli, S.; Albanese, D. Reductive Dehalogenation of α-Haloketones Promoted by Hydroiodic Acid and Without Solvent. *Synth. Commun.* **1993**, *23*, 1385−1391.
(17) (a) Kumar Saini, R.; Borpatra, P. J.; Kumar Pandey, S. I_2-DMSO-Mediated Cascade Cyclization of β-Ketosulfoxonium Ylides and β-Enaminones: Synthesis of Quaternary Carbon Centered 2-Hydroxy-pyrrol-3(2*H*)-ones. *Eur. J. Org. Chem.* **2023**, *26*, e202300693. (b) Jayram, J.; Xulu, B. A.; Jeena, V. Iodine/DMSO Promoted Oxidation of Benzylic $C_{sp}{}^3$−H Bonds to Diketones − A Mechanistic Investigation. *Tetrahedron.* **2019**, *75*, 130617. (c) Lian, M.; Li, Q.; Zhu, Y.; Yin, G.; Wu, A. Logic Design and Synthesis of Quinoxalines *via* the Integration of Iodination/Oxidation/Cyclization Sequences from Ketones and 1,2-Diamines. *Tetrahedron.* **2012**, *68*, 9598−9605.
(18) Tian, X.; Song, L.; Li, E.; Wang, Q.; Yu, W.; Chang, J. Metal-free One-Pot Synthesis of 1,3-Diazaheterocyclic Compounds *via* I_2-Mediated Oxidative C−N bond Formation. *RSC Adv.* **2015**, *5*, 62194−62201.
(19) Yadav, P.; Yadav, S.; Awasthi, A.; Phanindrudu, M.; Bhowmick, S.; Tiwari, D. K. DMSO As A Dual Carbon Synthon in One-pot Tandem Synthesis of *N*-Alkylated Quinazolinones from Anthranilamides and Acetophenones. *New J. Chem.* **2022**, *46*, 16289−16296.
(20) (a) Bandgar, B. P.; Shaikh, K. A. Molecular Iodine-Catalyzed Efficient and Highly Rapid Synthesis of Bis(indolyl)methanes under Mild Conditions. *Tetrahedron Lett.* **2003**, *44*, 1959−1961. (b) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. A Simple and Efficient Approach to the Synthesis of 2-Phenylquinazolines via sp3 C−H Functionalization. *Org. Lett.* **2010**, *12*, 2841−2843. (c) Jaratjaroonphong, J.; Sathalalai, S.; Techasauvapak, P.; Reutrakul, V. Iodine-Catalyzed Friedel−Crafts Alkylation of Electron-Rich Arenes with Aldehydes: Efficient Synthesis of Triarylmethanes and Diarylalkanes. *Tetrahedron Lett.* **2009**, *50*, 6012−6015.
(21) Zhu, Y.-P.; Fei, Z.; Liu, M.-C.; Jia, F.-C.; Wu, A.-X. Direct One-Pot Synthesis of Luotonin F and Analogues *via* Rational Logical Design. *Org. Lett.* **2013**, *15*, 378−381.
(22) (a) Wu, W.; Fan, S.; Wu, X.; Fang, L.; Zhu, J. Cobalt Homeostatic Catalysis for Coupling of Enaminones and Oxadiazolones to Quinazolinones. *J. Org. Chem.* **2023**, *88*, 1945−1962. (b) Abdullaha, M.; Mohammed, S.; Ali, M.; Kumar, A.; Vishwakarma, R. A.; Bharate, S. B. Discovery of Quinazolin-4 (3*H*)-ones as NLRP3 Inflammasome Inhibitors: Computational Design, Metal-free Synthesis, and *in vitro* Biological Evaluation. *J. Org. Chem.* **2019**, *84*, 5129−5140. (c) Hu, B.-Q.; Cui, J.; Wang, L.-X.; Tang, Y.-L.; Yang, L. Metal-Free Synthesis of Quinazolinones Without any Additives in Water. *RSC Adv.* **2016**, *6*, 43950−43953. (d) Sharma, R.; Vishwakarma, R. A.; Bharate, S. B. Ligand-Free Copper-Manganese Spinel Oxide-Catalyzed Tandem One-Pot C−H Amidation and *N*-Arylation of Benzylamines: A Facile Access to 2-Arylquinazolin-4(3*H*)-ones. *Adv. Synth. Catal.* **2016**, *358*, 3027−3033.
(23) Kumar, S.; Padala, K.; Maiti, B. H_2O_2-Mediated Synthesis of a Quinazolin-4(3*H*)-one Scaffold: A Sustainable Approach. *ACS Omega.* **2023**, *8*, 33058−33068.
(24) (a) Zhang, Y.; Xiong, W.; Chen, L.; Shao, Y.; Li, R.; Chen, Z.; Ge, J.; Lv, N.; Chen, J. Palladium-Catalyzed Cascade Reactions in Aqueous Media: Synthesis and Photophysical Properties of Pyrazino-Fused Quinazolinones. *Org. Chem. Front.* **2021**, *8*, 304−309. (b) Wang, Z. H.; Wang, H.; Wang, H.; Li, L.; Zhou, M. D. Ruthenium(II)-Catalyzed C−C/C−N Coupling of 2-Arylquinazolinones with Vinylene Carbonate: Access to Fused Quinazolinones. *Org. Lett.* **2021**, *23*, 995−999. (c) Lu, H.; Yang, Q.; Zhou, Y.; Guo, Y.; Deng, Z.; Ding, Q.; Peng, Y. Cross-Coupling/Annulations of Quinazolones with Alkynes for Access to Fused Polycyclic Heteroarenes Under Mild Conditions. *Org. Biomol. Chem.* **2014**, *12*, 758−764. (d) Guo, S.; Zhai, J.; Fan, X. An I_2-Mediated Cascade Reaction of 2′-Bromoacetophenones with Benzohydrazides/Benzamides Leading to Quinazolino [3,2-b] Cinnoline or Tryptanthrin Derivatives. *Org. Biomol. Chem.* **2017**, *15*, 1521−1529.

https://doi.org/10.1021/acs.joc.4c01354
J. Org. Chem. XXXX, XXX, XXX−XXX