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COMMUNICATION

Aerobic photooxidative synthesis of 2-aryl-4-quinazolinones from aromatic aldehydes and aminobenzamide using catalytic amounts of molecular iodine

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This study reports a safe, mild, and environmentally benign synthetic method toward 2-aryl-4-quinazolinones from aromatic aldehydes and aminobenzamides through a cyclization-oxidation sequence using a catalytic amount of iodine, which serves as both a Lewis acid and an oxidant, harmless visible light irradiation, and molecular oxygen as the terminal oxidant.

4-Quinazolinones are well-known compounds with a variety of biological and pharmacological activities, such as anticancer, anti-inflammatory, and antidiuretic, and are assigned as privileged structures in drug discovery.¹ As such, many methods have been reported for the synthesis of 4-quinazolinones.² Among those reported, oxidation of cyclic aminal intermediates obtained from 2-aminobenzamides and aldehydes with $I_{2,3}^{3}$ DDQ (dichlorodicyanobenzoquinone),⁴ CuCl₂,⁵ CuBr,⁶ MnO₂,⁷ KMnO₄,⁸ FeCl₃•6H₂O,⁹ or microwave irradiation conditions^{10,4b} are reliable methods; however, they require stoichiometric amounts of reagents, transition metals, or involve a complicated procedure.

In recent times, iodine source catalyzed C–H oxidation with various stoichiometric oxidants, such as H_2O_2 or *tert*-BuOOH, and has attracted great interest because iodine sources have low toxicity and are inexpensive compared with transition metal catalysts.¹¹ Furthermore, iodine serves as both a Lewis acid and an oxidant.¹² Therefore, in multi-step syntheses, iodine is able to accelerate stoichiometric or catalytic domino reactions.¹³

From the perspective of green chemistry, various aerobic photooxidative reactions using catalytic amounts of iodine sources with molecular oxygen as the terminal oxidant under visible light irradiation have been developed in our laboratory.¹⁴ The methods to synthesize the quinazolinones using molecular oxygen were recently reported but they

require transition metals or thermal condition.¹⁵ As such, we developed an aerobic photooxidative synthesis of 2-aryl-4quinazolinones from aromatic aldehydes and aminobenzamide using a catalytic amount of iodine with more mild condition (Scheme 1). Herein we describe this reaction in detail.



Scheme 1. Catalytic aerobic photooxidative syntheses of 4-quinazolinones

We selected 2-aminobenzamide (1) and benzaldehyde (2a) as the test substrates for optimization of the reaction conditions (Table 1). Although we examined the reaction conditions with various halogen sources, the yields of 2phenyl-4-quinazolinone (3a) were unsatisfactory, except for those using molecular iodine (entries 1-6). In this reaction, addition of K₂CO₃ or Na₂SO₄ had only a marginal effect (entries 13 and 14), while addition of AcOH decreased the yield of 3a to 17% (entry 15). Further study of the solvent, amount of benzaldehyde, and reaction time revealed that using iodine (0.05 equiv) and benzaldehyde (1.0 equiv) in EtOAc for 1 h gave the best yield (entry 17). The fact that 3a was not obtained or was obtained only in low yield without iodine, molecular oxygen, or photoirradiation shows the necessity of these conditions for this reaction (entries 18-20). Under these conditions, 1 and the cyclized intermediate (2,3-dihydro-2phenyl-4(1H)-quinazolinone: 4a) were obtained in low yields.

Table 2 shows the results of the scope and limitations of photooxidative synthesis of 2-aryl-4-quinazolinones from various aromatic aldehydes under the optimized conditions. In general, the corresponding 2-aryl-4-quinazolinones were obtained in moderate to high yields regardless of the electron donating or weak electron withdrawing groups on the benzene ring of the aldehydes (entries 1–8). In contrast, 4-cyano and 4-nitrobenzaldehyde bearing strong electron withdrawing groups gave moderate and low yields of **3**. Unfortunately, aliphatic aldehydes such as cyclohexanecarboxaldehyde and dodecyl aldehyde were poor substrates.

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⁺ Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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 Table 1. Optimization of the reaction conditions for the synthesis of 2-aryl-4quinazolinones

	0 └──NH₂ + PhCł NH₂ 1 2a (1.5 e	HO Haloge HO ac	O₂, hv (VIS) en source (0.05 eq dditive (0.1 equiv) solvent, 30 min	uiv) V N N N N N N N N N N N N N
entry	halogen source	additive	solvent	yield (%) ^a
1	KI	-	EtOAc	0
2	Lil	-	EtOAc	0
3	Cal ₂	-	EtOAc	0
4	Znl ₂	-	EtOAc	6
5	I ₂	-	EtOAc	86
6	I ₂	-	MeOH	74
7	I ₂	-	<i>i</i> -Pr ₂ O	24
8	I ₂	-	Hexane	22
9	I ₂	-	H ₂ O	11
10	I ₂	-	MeCN	6
11	I ₂	-	Acetone	0
12	I ₂	K ₂ CO ₃	EtOAc	76
13	I ₂	Na_2SO_4	EtOAc	73
14	I ₂	AcOH	EtOAc	17
15 ^b	I ₂	-	EtOAc	85 (86) ^c
16 ^d	-	-	EtOAc	0
17 ^e	I ₂	-	EtOAc	0
18 ^f	I ₂	-	EtOAc	trace

^{*a*} The reaction conditions: **1** (0.3 mmol), **2a** (1.5 equiv), and halogen sources (0.05 equiv) in solvent (5 mL) was stirred and irradiated with fluorescent lamp under O₂ atmosphere for 30 min. ¹H NMR yields. ^{*b*} Reaction was conducted for 1h and conducted with 1.0 equivalent of benzaldehyde. ^{*c*} The number in the parentheses is the isolated yield. ^{*d*} **1** (26%) was recovered with **4a** (16%). ^{*f*} Reaction was conducted in the dark. **1** (18%) was recovered with **4a** (28%).

To clarify the reaction mechanism, several control experiments were examined. When one equivalent of molecular iodine was used in the absence of molecular oxygen and visible light irradiation, 3a was obtained in low yield and many by-products were formed (Scheme 2, equation 1). This result indicated that the reaction required irradiation with visible light and the presence of molecular oxygen. When 4a was used as a substrate under the optimal conditions, 3a was obtained in good yield (Scheme 2, equation 2). In contrast, no 3a was obtained in the absence of iodine (Scheme 2, equation 3). These results and entries 18-20 in Table 2 suggest that 4a is the reaction intermediate and molecular oxygen, iodine, and visible light are all required for the oxidation of 4a. Hypoiodous acid (IOH) may be the active species in the final step of the oxidation because it is easily prepared from an iodine source and a peroxide.¹⁶

Scheme 3 shows a plausible path for this reaction. The intermediates (4) are formed through condensation between 2-aminobenzamides (1) and aldehydes (2), catalyzed by molecular iodine as a Lewis acid. Intermediate 4 is then transformed to 4-quinazolinones (3) by oxidation with molecular iodine, molecular oxygen, and visible light. In addition, hydrogen iodide, generated by the oxidation of 4, is reoxidized to molecular iodine under the aerobic photooxidative conditions.

Table 2. Catalytic aerobic photooxidative synthesis of 2-aryl-4-quinazolinones

	O [⊥] NH ₂ + R'-1 NH ₂ ⊨ 2 (L, CHO 1.0 equiv)	O ₂ , <i>h</i> v (VIS) I ₂ (0.05 equiv) EtOAc (5 mL)		H R'
entry	R'		time (h)	product	yield (%) a
1	н	2a	1	3a	86
2	4-OH	2b	5	3b	80
3	4-OMe	2c	1	3c	75
4	3-OMe	2d	1	3d	81
5	4-Me	2e	5	3e	76
6	3-Me	2f	10	3f	93
7	4- ^t Bu	2g	3	3g	83
8	4-F	2h	15	3h	85
9	4-Cl	2i	15	3i	88
10	4-Br	2j	15	3j	82
11	4-CF ₃	2k	15	3k	76
12	4-CN	21	5	31	66
13	4-NO ₂	2m	5	3m	69

 $^{\alpha}$ The reaction conditions: 1 (0.3 mmol), 2 (1.0 equiv), and ${\sf I}_2$ (0.05 equiv) in EtOAc (5 mL) was stirred and irradiated with fluorescent lamp under O_2 atmosphere. Isolated yields .







Scheme 3. Plausible pathway of photooxidative synthesis of 2-aryl-4-quinazolinones

Conclusions

In conclusion, we have developed an environmentally benign synthesis of 2-aryl-4-quinazolinones with a catalytic amount of iodine under photooxidative conditions. This method is of Published on 21 July 2015. Downloaded by Yale University Library on 22/07/2015 06:22:46.

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interest in green chemistry because of the use of molecular oxygen and visible light irradiation.

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