# **ARTICLE IN PRESS**

Chinese Chemical Letters xxx (2019) xxx-xxx



Contents lists available at ScienceDirect

### **Chinese Chemical Letters**



journal homepage: www.elsevier.com/locate/cclet

### Communication

## Ir-catalyzed regiospecific mono-sulfamidation of arylquinazolinones

Yadong Feng<sup>a,b,\*</sup>, Zhenyue Zhang<sup>b</sup>, Qi Fu<sup>a</sup>, Qiuhong Yao<sup>a</sup>, Huabin Huang<sup>a</sup>, Jinhai Shen<sup>a</sup>, Xiuling Cui<sup>b,\*\*</sup>

<sup>a</sup> College of Environment and Public Health, Xiamen Huaxia University, Xiamen 361024, China
<sup>b</sup> Engineering Research Center of Molecular Medicine of Ministry of Education, Key Laboratory of Fujian Molecular Medicine, Key Laboratory of Xiamen Marine and Gene Drugs, School of Biomedical Sciences, Huaqiao University, Xiamen 361021, China

#### ARTICLE INFO

Article history: Received 26 March 2019 Received in revised form 24 April 2019 Accepted 7 May 2019 Available online xxx

Keywords: Ir-catalyzed C-H activation Mono-sulfamidation Selectivity Arylquinazolinones

### ABSTRACT

An Ir-catalyzed selective mono-sulfamidation of 2-arylquinazolinones has been achieved with a low catalyst loading under mild conditions. A series of regioselective mono-sulfamided 2-arylquinazolinones were obtained in up to 90% yields. Compared with our previous work of constructing di-sulfamidated 2-arylquinazolinones, the mono-sulfamided products could be obtained selectively by changing the ratio of substrates, the loading of catalyst, acid additive, and reaction time.

© 2019 Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences. Published by Elsevier B.V. All rights reserved.

Quinazolinone is ubiquitous framework in drugs and natural products because of their various biological activities [1]. As a result, the construction and modification of guinazolinones have been attractive for the organic chemists. Our group has developed a copper-catalyzed synthesis of quinazolinones from easily available 2-arylindoles and amines or ammoniums in 2015 [2]. In 2016, Huang group reported a Cu-catalyzed domino reaction for the synthesis of pyrido-fused quinazolinone derivatives, which involved C-N/C-C bond cleavage and two C-N bond formations in a one-pot operation [3]. In 2018, Su group developed an Au-catalyzed selective cyclization of alkynyl quinazolinonetethered pyrroles for the synthesis of fused quinazolinone scaffolds [4]. Chen group developed a Pd-catalyzed tandem reaction of quinazolinone-based nitriles with arylboronic acids for the synthesis of 2-(4-arylquinazolin-2-yl)anilines [5]. Great process on transition metal-catalyzed functionalization of C-H bond has been achieved during past decade to obtain various guinazolinone derivatives. For example, in 2017, Mhaske group reported a Pdcatalyzed mono-arylation of aromatic rings by C-H bond activation using quinazolinone as the inherent directing group, in which Na<sub>2</sub>CO<sub>3</sub> was found to be crucial for this transformation [6]. Moreover, the same group developed a Ru-catalyzed

Corresponding author. E-mail addresses: fengyd@hxxy.edu.cn (Y. Feng), cuixl@hqu.edu.cn (X. Cui). alkenylation/tandem hydroamidative cyclization of quinazolinones leading to the selective mono- or di-alkenylation products [7]. In 2018, Jana group has developed a Ru-catalyzed redoxneutral C—H bond allylation/hydroamination cascade reaction to synthesize dihydroisoquinolino[1,2-b]quinazolinones [8]. For this direction, our group reported a Pd-catalyzed aerobic oxidative reaction of arylquinazolinones with alkynes to assemble fusedpolycyclic systems containing tetrahydropyridine and dihydrofuran rings [9]. On the other hand, organic azides have been extensively explored in C-H amination or amidation reactions for their ability to act as an internal oxidant and environmentally benign reagent [10]. For example, Chang group reported the first intermolecular amidation of arenes with sulfonyl azides via Rhcatalyzed C-H activation in 2012 [11]. Subsequently, in 2013, Glorius group reported a Rh/Cu-cocatalyzed synthesis of indazoles through C-H amidation and N-N bond formation from arylimidates and organo azides [12]. After that, the groups of Ackermann, Kanai, Wang, Li, Cui, and Zhu have reported many other similar strategies for C-N bond construction via C-H amination or amidation reactions using organic azides [13]. However, controlling site selectivity is still one of the challenges in these current reactions. Recently, our group has developed an Ircatalyzed direct di-sulfamidation of arylquinazolinones using sulfonyl azides as amino sources (Scheme 1a) [14]. However, it is not easy to regioselectivity obtain mono-substituted products in the metal-catalyzed arylation, alkenylation, allylation or sulfamidation of quinazolinones, in which additives, such as acid and base, were necessary for the transformations. In our continuing effort to

1001-8417/© 2019 Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences. Published by Elsevier B.V. All rights reserved.

Please cite this article in press as: Y. Feng, et al., Ir-catalyzed regiospecific mono-sulfamidation of arylquinazolinones, Chin. Chem. Lett. (2019), https://doi.org/10.1016/j.cclet.2019.05.013

<sup>\*</sup> Corresponding author at: College of Environment and Public Health, Xiamen Huaxia University, Xiamen 361024, China.

https://doi.org/10.1016/j.cclet.2019.05.013

# **ARTICLE IN PRESS**

Y. Feng et al./Chinese Chemical Letters xxx (2019) xxx-xxx

(a) previous work:



Scheme 1. Ir-catalyzed direct amidation of 2-arylquinazolinones.

develop efficient methods controlling site selectivity in C–H bond activation [15], herein, we disclose an Ir-catalyzed direct monoamidation of 2-arylquinazolinones with sulfonyl azides to produce *ortho*-amided quinazolinones (Scheme 1b), in which monosulfamidated products were selectively obtained with high yields by changing the ratio of substrates, the loading of catalyst, acid additive and reaction time.

Initially, the amidation of 2-phenylquinazolin-4(3*H*)-one (**1a**) (0.20 mmol) with *para*-toluenesulfonyl azide (**2a**) (0.20 mmol) was chosen as a model reaction to examine the impact of various parameters on the reaction (Table 1). The results revealed that monoamidated 2-phenylquinazolin-4(3*H*)-one (**3a**) and diamidated 2-phenylquinazolin-4(3*H*)-one (**4a**) were obtained in 40% and 23% yield respectively in DCE (1,2-dichloroethane) at 80 °C when [IrCp\*Cl<sub>2</sub>]<sub>2</sub> (1.0 mol%) was used as a catalyst with AgSbF<sub>6</sub> (4.0 mol%), TFA (4.0 equiv.) under air (Table 1, entry 1). When the loading amount of [IrCp\*Cl<sub>2</sub>]<sub>2</sub> and AgSbF<sub>6</sub> were changed to 2.0 mol% and 8.0 mol%, the yield of **3a** was increased to 55% as well as 19% yield of **4a** (Table 1, entry 1 *vs.* entries 2–5). Notably, when AcOH was chosen as the acid additive instead of TFA, the yield of **4a** could

Table 1



Entry	[IrCp*Cl <sub>2</sub> ] <sub>2</sub> (mol	AgSbF <sub>6</sub> (mol	Acid (equiv.)	t (h)	Yield (%) <sup>b</sup>	
	%)	%)			3a	4a
1	1.0	4.0	TFA (4.0)	2.5	40	23
2	0.5	2.0	TFA (4.0)	2.5	36	18
3	1.5	6.0	TFA (4.0)	2.5	51	20
4	2.0	8.0	TFA (4.0)	2.5	55	19
5	2.5	10.0	TFA (4.0)	2.5	52	22
6	2.0	8.0	AcOH (4.0)	2.5	63	12
7	2.0	8.0	TfOH (4.0)	2.5	nd	nd
8	2.0	8.0	PhCOOH	2.5	nd	nd
			(4.0)			
9	2.0	8.0	AcOH (3.0)	2.5	50	8
10	2.0	8.0	AcOH (5.0)	2.5	71	trace
11	2.0	8.0	AcOH (6.0)	2.5	70	trace
12	2.0	8.0	AcOH (5.0)	3.0	69	trace
13	2.0	8.0	AcOH (5.0)	2.0	77	trace
14	2.0	8.0	AcOH (5.0)	1.5	83	trace
15	2.0	8.0	AcOH (5.0)	1.0	90	trace
16	2.0	8.0	AcOH (5.0)	0.5	62	trace

 $^a$  Reaction conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), 80  $^\circ$ C, DCE (2.0 mL), air.  $^b$  Isolated yields. nd=not detected.

be reduced to trace, and the yield of **3a** was selectively increased to 71% when 5.0 equiv. of AcOH was introduced into the reaction (Table 1, entry 1 vs. entries 6–11). Moreover, the yield of **3a** could be increased to 90% when the reaction time was reduced to 1.0 h (Table 1, entries 12–16). Based on the results, under the optimum reaction conditions, the target product **3a** was obtained selectively in 90% yield in DCE at 80 °C when [IrCp\*Cl<sub>2</sub>]<sub>2</sub> (2 mol%) was used as a catalyst with AgSbF<sub>6</sub> (8.0 mol%), AcOH (5.0 equiv.) under air for 1.0 h (Table 1, entry 15), and the yield of **4a** was reduced to trace.

With the optimized reaction conditions in hand, the scope of the substrates was examined (Table 2). First, toluenesulfonyl azide (2a) reacted smoothly with 2-phenylquinazolin-4(3H)-one (1a) and its derivatives (1b-m) to give 3a-m in good to excellent yields (45%–90%). 6-Cl, 6–OCH<sub>3</sub>, and 5-F substituted arylquinazolinones could provide the corresponding products **3b–3d** in 83%, 68% and 45% yields, respectively. F group at the 2- and 4-position of 2phenyl in 2-aryl-quinazolin-4(3H)-one provided the corresponding products 3e and 3f in 84% and 90% yields, which indicated that steric effect did not significantly affect this transformation. Other groups, such as Cl, Br, CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>3</sub>, and NO<sub>2</sub> could be well tolerated and gave the corresponding products in satisfactory yields (**3g-l**) (65%–87%). It can be seen that the electron density on the 2-arylquinazolinones did not significantly affect the efficiency of the reaction as well. The reaction did not occur when quinazolinones with both ortho-positions of aryl ring were substituted, such as 2-(2,6-dimethylphenyl)quinazolin-4(3H)one. Meanwhile, 2-phenylquinazolin-4(3H)-one (1a) also reacted smoothly with benzenesulfonyl azide (2b) to give the desired product **3m** in 85% vield. Moreover, when other groups, such as methyl, 4-methoxyphenyl, benzoyl, and 4-nitrophenyl are chosen as R<sup>3</sup> in this reaction, the yields of corresponding products are very low, and di-sulfamided 2-arylquinazolinones were detected as main products.

Based on the results obtained and literatures [16], the proposed mechanism was the same with the first catalytic cycle in the reaction for di-sulfamidated arylquinazolinones and was not described again here (Scheme 2). However, it was noteworthy that changing acid additive stopped the reaction in the first catalytic cycle, because AcOH was too weak to stabilize the metal intermediate in sequential two C–H bonds activation. At the same time, increasing the loading of catalyst and reducing the reaction time could assist the first C–H bond activation to proceed more thoroughly.

In summary, we have demonstrated an Ir-catalyzed selective mono-sulfamidation of 2-arylquinazolinones with a low catalyst

 $\begin{array}{c} \textbf{Table 2} \\ \text{Scope of substrates} & \overset{a}{=} \kappa^{t} \left( \int_{1}^{N} N_{1}^{t} + \int_{1}^{R} \rho_{1}^{t} \rho_{2}^{t} \rho_{3}^{t} \rho_$ 

Entry	1	$\mathbb{R}^1$	$\mathbb{R}^2$	R <sup>3</sup>	3	Yield (%) <sup>b</sup>
1	1a	Н	Н	CH <sub>3</sub>	3a	90
2	1b	6-Cl	Н	$CH_3$	3b	83
3	1c	6-OCH <sub>3</sub>	Н	$CH_3$	3c	68
4	1d	5-F	Н	CH <sub>3</sub>	3d	45
5	1e	Н	2-F	CH <sub>3</sub>	3e	84
6	1f	Н	4-F	$CH_3$	3f	90
7	1g	Н	4-Cl	$CH_3$	3g	78
8	1h	Н	4-Br	$CH_3$	3h	82
9	1i	Н	$4-CH_3$	$CH_3$	3i	77
10	1j	Н	4-CF <sub>3</sub>	$CH_3$	3j	87
11	1k	Н	4-0CH <sub>3</sub>	CH <sub>3</sub>	3k	83
12	11	Н	4-NO <sub>2</sub>	CH <sub>3</sub>	31	65
13	1a	Н	Н	Н	3 m	85

<sup>a</sup> Reaction conditions: 1 (0.20 mmol), 2 (0.2 mmol), Ir (2.0 mol %), Ag (8.0 mol %), AcOH (5.0 equiv), DCE (2.0 mL), air.
 <sup>b</sup> Isolated yields.

2

### Y. Feng et al./Chinese Chemical Letters xxx (2019) xxx-xxx



Scheme 2. The proposed reaction mechanism.

loading under mild conditions. A series of mono-sulfamided 2-arylquinazolinones were obtained in up to 90% yields. Compared with our previous work, the mono-sulfamided products could be obtained selectively by changing the ratio of substrates, the loading of catalyst, acid additive, and reaction time, which could be explained reasonably by the reaction mechanism. Further study on the application of this reaction is ongoing in our laboratory.

### Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 21572072), Xiamen Southern Oceanographic Center (No. 15PYY052SF01), 111 Project (No. BC2018061) and Y. Feng thanks the Postgraduates Innovative Fund in Scientific Research of Huaqiao University and, the financial support of Scientific Research Foundation of Xiamen Huaxia University (No. HX201807), Outstanding Youth Scientific Research Cultivation Plan in Fujian Province University (2018).

### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j. cclet.2019.05.013.

### References

- [1] (a) A.K. Nanda, S. Ganguli, R. Chakraborty, Molecules 12 (2007) 2413-2426; (b) J.H. Chan, J.S. Hong, L.F. Kuyper, et al., J. Med. Chem. 38 (1995) 3608-3616; (c) H. Kikuchi, K. Yamamoto, S. Horoiwa, et al., J. Med. Chem. 49 (2006) 4698-4706:
  - (d) M.H. Yen, J.R. Sheu, I.H. Peng, Y.M. Lee, J.W.J. Chern, Pharm. Pharmacol. 48 (1996) 90-95;
  - (e) A. Archana, V.K. Shrivastava, R. Chandra, A. Kumar, Indian J. Chem. 41B (2002) 2371-2375;
  - (f) J. Kunes, J. Bazant, M. Pour, K. Waisser, M. Slosarek, J. Janota, Farmaco. 55 (2000) 725-729;
  - (g) K. Waisser, J. Gregor, H. Dostal, et al., Farmaco 56 (2001) 803-807;
  - (h) Y. Takase, T. Saeki, N. Watanabe, et al., J. Med. Chem. 37 (1994) 2106-2111; (i) M. Dupuy, F. Pinguet, O. Chavignon, et al., Chem. Pharm. Bull. 49 (2001) 1061-1065:
  - (j) P.M. Chandrika, T. Yakaiah, A.R.R. Rao, et al., Eur. J. Med. Chem. 43 (2008) 846-852.
- [2] Y. Feng, Y. Li, G. Cheng, L. Wang, X. Cui, J. Org. Chem. 80 (2015) 7099-7107.
- [3] M. Liu, M. Shu, C. Yao, G. Yin, D. Wang, J. Huang, Org. Lett. 18 (2016) 824-827.
- [4] L. Wei, G. He, X. Kong, et al., J. Org. Chem. 83 (2018) 6719-6727.
- [5] Y. Zhang, Y. Shao, J. Gong, et al., Adv. Synth. Catal. 17 (2018) 3260-3265. [6] D.N. Garad, A.B. Viveki, S.B. Mhaske, J. Org. Chem. 12 (2017) 6366-6372.
- [7] A.B. Viveki, S.B. Mhaske, J. Org. Chem. 16 (2018) 8906-8913.
- [8] G. Bairy, S. Das, H.M. Begam, R. Jana, Org. Lett. 20 (2018) 7107-7112.
- [9] Y. Feng, N. Tian, Y. Li, et al., Org. Lett. 19 (2017) 1658-1661.
- [10] (a) J. Kim, S. Chang, Angew. Chem. Int. Ed. 53 (2014) 2203-2207;
- (b) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, J. Am. Chem. Soc. 136 (2014) 4141-4144:
- (c) H. Hwang, J. Kim, J. Jeong, S. Chang, J. Am. Chem. Soc. 136 (2014) 10770-10776;
- (d) C. Pi, X. Cui, Y. Wu, J. Org. Chem. 80 (2015) 7333-7339;
- (e) B. Zhu, X. Cui, C. Pi, D. Chen, Y. Wu, Adv. Synth. Catal. 358 (2016) 326–332; (f) Y. Park, Y. Kim, S. Chang, Chem. Rev. 117 (2017) 9247-9301;
- (g) D. Lee, Y. Kim, S. Chang, J. Org. Chem. 78 (2013) 11102-11109;
- (h) T. Kang, H. Kim, J.G. Kim, S. Chang, Chem. Commun. 50 (2014) 12073-12075:
- (i) H. Kim, G. Park, J. Park, S. Chang, ACS Catal. 6 (2016) 5922-5929.
- [11] J.Y. Kim, S.H. Park, J. Ryu, et al., J. Am. Chem. Soc. 134 (2012) 9110-9113.
- [12] D.G. Yu, M. Suri, F. Glorius, J. Am. Chem. Soc. 135 (2013) 8802-8805.
- [13] (a) V.S. Thirunavukkarasu, K. Raghuvanshi, L. Ackermann, Org. Lett. 15 (2013) 3286-3289:

(b) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, Adv. Synth. Catal. 356 (2014) 1491-1495; (c) N. Wang, R. Li, L. Li, et al., J. Org. Chem. 79 (2014) 5379-5385; (d) B. Zhou, Y. Yang, J. Shi, H. Feng, Y. Li, Chem. Eur. J. 19 (2013) 10511–10515;

- (e) M.E. Wei, L.H. Wang, Y.Y. Li, X. Cui, Chin. Chem. Lett. 26 (2015) 1336-1340; (f) C. Pan, N. Jin, H. Zhang, J. Han, C. Zhu, J. Org. Chem. 79 (2014) 9427-9432.
- [14] Y. Feng, Y. Li, Y. Yu, L. Wang, X. Cui, RSC Adv. 8 (2018) 8450-8454.
- [15] (a) L. Wang, D. Xiong, L. Jie, C. Yu, X. Cui, Chin. Chem. Lett. 29 (2018) 907–910; (b) T. Yuan, C. Pi, C. You, et al., Chem. Commun. 52 (2019) 129-258; (c) L. Xu, T. Li, L. Wang, X. Cui, J. Org. Chem. 84 (2019) 560-567; (d) Z. Yang, L. Jie, Z. Yao, Z. Yang, X. Cui, Adv. Catal. Synth. 1 (2019) 214–218; (e) M. Gao, Y. Li, L. Xie, R. Chauvin, X. Cui, Chem. Commun. 52 (2016) 2846-2849: (f) Y. Yu, Y. Feng, R. Chauvin, et al., Org. Lett. 20 (2018) 4209–4212; (g) Y. Li, C. Jia, H. Li, et al., Org. Lett. 20 (2018) 4930–4933;
  - (h) L. Jie, L. Wang, D. Xiong, et al., J. Org. Chem. 83 (2018) 10974-10984:
  - (i) L. Xu, L. Wang, Y. Feng, et al., Org. Lett. 19 (2017) 4343-4346.
- [16] (a) J. Ryu, K. Shin, S.H. Park, J.Y. Kim, S. Chang, Angew. Chem. Int. Ed. 51 (2012) 9904-9908:

(b) K. Shin, Y. Baek, S. Chang, Angew. Chem. Int. Ed. 52 (2013) 8031-8036; (c) J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, J. Am. Chem. Soc. 135 (2013) 12861-12868.