EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Copper-Catalyzed Direct Carbamoylation of Quinoxalin-2(1H)-Ones with Hydrazinecarboxamides under Mild Conditions

Authors: Xianglong Chu, Yujuan Wu, Haigen Lu, and Chen Ma

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901858

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901858

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201901858

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Copper-Catalyzed Direct Carbamoylation of Quinoxalin-2(1*H*)-Ones with Hydrazinecarboxamides under Mild Conditions

Xianglong Chu,[a] Yujuan Wu,[a] Haigen Lu,[a] Bingchuan Yang[b]* and Chen Ma[a]*

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract: A direct C-H bond carbamoylation of quinoxalin-2(1*H*)-ones with hydrazinecarboxamides has been developed. This reaction provides a series of 3-carbamoylquinoxalin-2(1*H*)-one derivatives in moderate to good yields under mild conditions with a broad range of substrates and functional group tolerance. The present methodology affords a convenient and practical access to pharmaceutically active 3-carbamoylquinoxalin-2(1*H*)-one derivatives.

The quinoxalin-2(1*H*)-one derivatives have attracted tremendous attention due to pharmaceutically important molecules[1] and outstanding biological properties.[2] Morever, 3-carbamoylquinoxalin-2(1*H*)-one derivative as an important pharmacophore has shown numerous signifigance biological properties.[3] Examples include the c-Met kinase inhibitors,[4] small-molecule HCV inhibitors,[5] PDE4 inhibitors[6] and anti-cancer properties[7] (Figure 1).

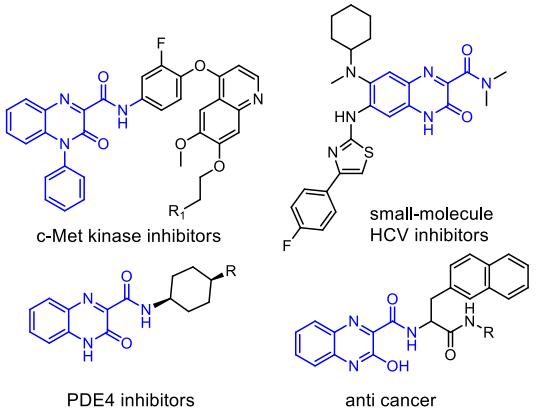
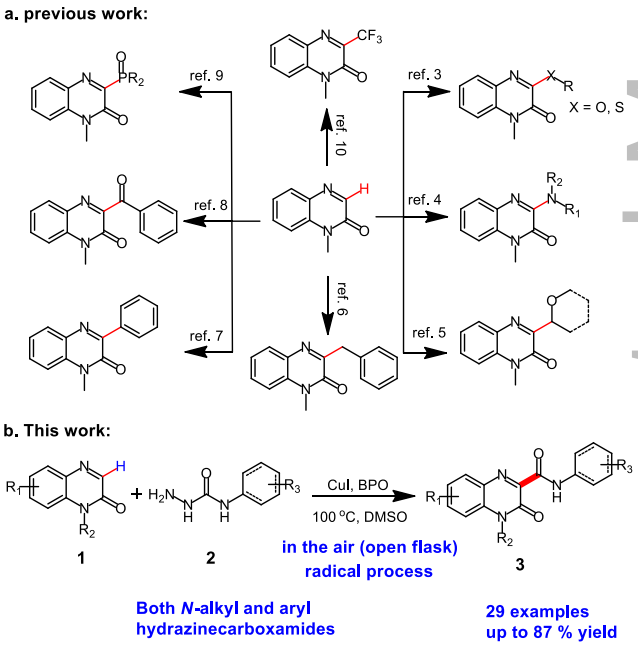


Figure 1. Pharmaceutically active 3-carbamoylquinoxalin-2(1*H*)-one derivatives.

[a] Dr. Xianglong Chu, Yujuan Wu, Haigen Lu, Dr. Bingchuan Yang* and Prof. Dr. Chen Ma*
school of Chemistry and Chemical Engineering, Shandong University, Jinan, 250100, P R China
E-mail: chenma@sdu.edu.cn
[b] School of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng, 252059, PR China
E-mail: yangbingchuan@lcu.edu.cn
Supporting information for this article is given via a link at the end of the document.

In view of their remarkable importance, the direct functionalization of C3 position of quinoxalin-2(1*H*)-one has been extensively studied in recent organic synthesis, for instance (Scheme 1a), etherification,[8] amination,[9] alkylation,[10] benzylation,[11] arylation,[12] acylation,[13] phosphonation,[14] trifluoromethylation.[15] Although remarkable achievements have been obtained, the direct C_3-H carbamoylation of quinoxalin-2(1*H*)-ones remains scarce. Due to importance of the 3-carbamoylquinoxalin-2(1*H*)-one derivatives, the development of a direct and simple method for synthesis of 3-carbamoylated quinoxalin-2(1*H*)-one derivatives is still highly desirable.



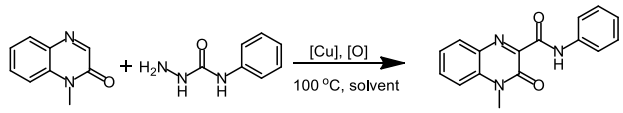
Scheme 1. Synthesis of 3-functionalized quinoxalin-2(1*H*)-one derivatives.

Amide bond linkage is one of the most essential unit omnipresent in many organic molecules including proteins,[16] natural alkaloids,[17] fine chemicals and pharmaceuticals.[18] About 60% of reactions (including 7.2% of peptide synthesis and 50% of amide-bond coupling) belong to amide bond formation in current medicinal chemistry according to litreature (2014) reported.[19] It is notable that carboxamide is the most abundant functional group in pharmaceutical structure, more than 25% drug

10.1002/ejoc.201901858

molecules contain at least one amide functional group.[20] In classical amide-bond formation, the activation of carboxylic acid or employment of novel catalyst is usually necessary.[21] However, there are several drawbacks in the classic synthetic methods of amides, including too much reaction waste, requirement of prefunctionalized starting materials, harsh reaction conditions and limited substrate scope. In additation, it has always been difficult to synthesize sterically hindered amide. Therefore, the developement of novel and efficient synthetic methods for the direct formation of 3-carbamoylated quinoxalin-2(1*H*)-one derivatives is in high demand. In continuation of our previous efforts on direct C-H bond functionalization,[22] we herein report our recent work on direct carbamoylation of quinoxalin-2(1*H*)-ones with hydrazinecarboxamides by a *N*-acyl radical process (scheme 1b), this protocol features without the necessary for pre-activation of reactant, broad substrate scope and moderate to good yields. To the best of our knowledge, direct carbamoylation on the C3 position of quinoxalin-2(1*H*)-one has not been reported. It is worthy to be noticed that sterically hindered amides can be smoothly introduced at C3 position of quinoxalin-2(1*H*)-one in our reaction system.

Table 1. Optimization of quinoxalin-2(1*H*)-ones with hydrazinecarboxamides.[a], [b]



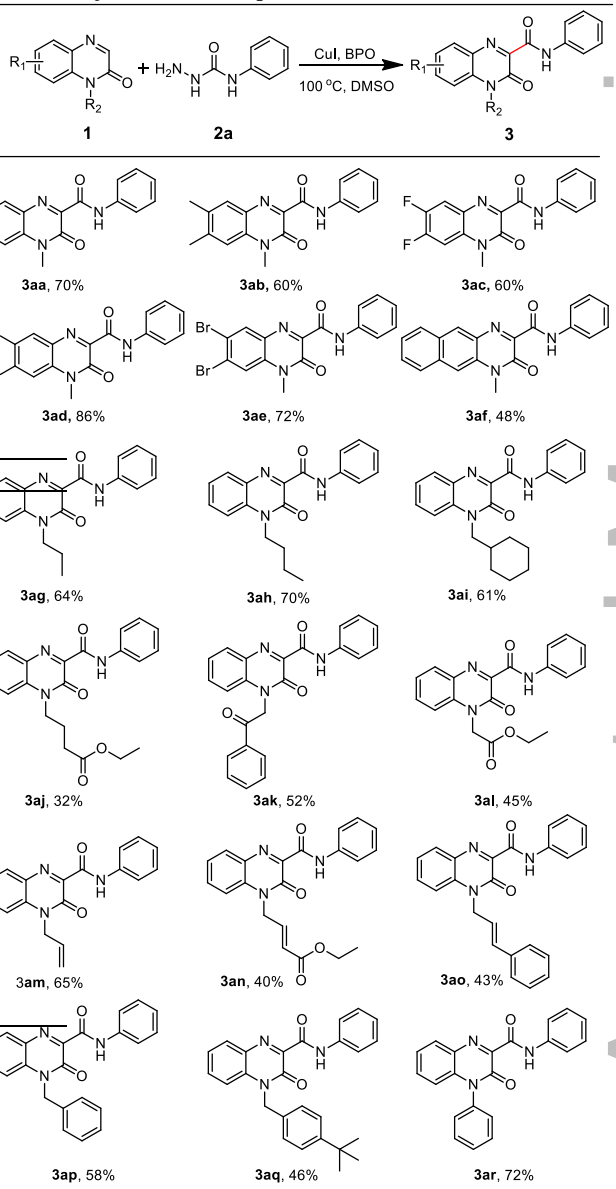
1a **2a** **3aa**

entry	[Cu]	[O]	solvent	yield, %[b]
1	CuBr	TBHP	DMSO	31
2	-	TBHP	DMSO	-
3	I_2	TBHP	DMSO	Trace
4	$Cu(OAc)_2•H_2O$	TBHP	DMSO	47
5	CuCl	TBHP	DMSO	38
6	$Cu(OAc)_2$	TBHP	DMSO	40
7	CuI	TBHP	DMSO	56
8	**CuI**	**BPO**	**DMSO**	**70**
9	CuI	TBPB	DMSO	29
10	CuI	DTBP	DMSO	-
11	CuI	$(NH_4)_2S_2O_8$	DMSO	-
12	CuI	BPO	DMSO/H_2O = 2:1	39
13	CuI	BPO	Dioxane	27
14	CuI	BPO	DMF	-
15	CuI	BPO	Toluene	20

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), [Cu] (0.02 mmol), [O] (0.6 mmol), solvent (1.5 mL), 100 °C, 18 h.
[b] Isolated yield.

Initially, we selected 1-methylquinoxalin-2(1*H*)-one (**1a**) as a model substrate to react with *N*-phenylhydrazinecarboxamide (**2a**) in the presence of 10 mol% of CuBr, 3 equivalent of *tert*-butyl hydroperoxide (TBHP) in DMSO at 100 °C. To our delight, the desired 4-methyl-3-oxo-*N*-phenyl-3,4-dihydroquinoxaline-2-carboxamide product (**3aa**) was obtained in 31% yield (Table 1, entry 1). The catalyst was proven to be essential for this transformation (Table 1, entry 2), and the copper was much more effective than iodine (Table 1, entry 3). Various copper catalysts were then investigated, and CuI exhibited the best effciency to afford **3aa** in 56% yield (Table 1, entries 4-7). The subsequent screening of oxidants showed that among the various oxidants (dibenzoyl peroxide (BPO), *tert*-butyl peroxybenzoate, di-*t-butyl* peroxide and $(NH_4)_2S_2O_8$), BPO showed the best efficiency (Table 1, entries 8-11). Finally, other solvents (DMSO: H_2O, dioxane, DMF, toluene) were used instead of DMSO, giving a decreased yield of **3aa** (Table 1, entries 12-15). Thus, we chose **1a** (0.2 mmol), **2a** (3.0 equiv.) 10 mol% of CuI and 3 equivalent of BPO in 1.5 mL DMSO at 100 °C for 18 hours as the optimal reaction conditions.

Table 2. Synthesis of the products **3aa**–**3ar**. [a],[b]

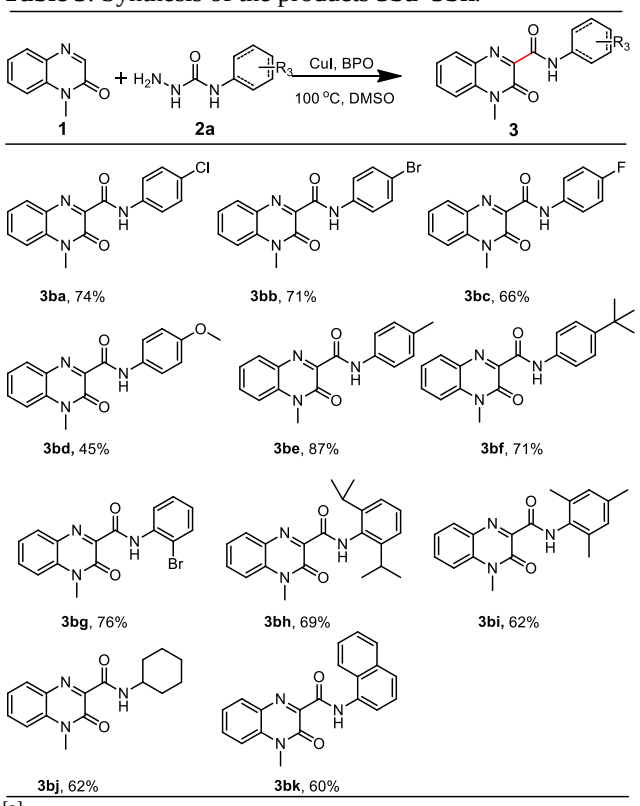


[a] Unless specifically noted otherwise, reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), CuI (0.02 mmol), BPO (0.6 mmol), solvent (1.5 mL), 100 °C, 18 h.
[b] Isolated yield.

With the optimized reaction conditions in hand, we explored the reaction of **2a** with various quinoxalin-2(1*H*)-

ones under the standard conditions. The results were shown in Table 2. First, we investigated the substitution at R_1 with R_2 = CH_3. A series of quinoxalin-2(1*H*)-ones with different electronic properties smoothly underwent the reaction, the corresponding compounds were obtained in 60-86% yields (Table 2, **3aa**-**3ae**). Generally, electron-withdrawing substituents on the aromatic ring has positive effect on the yield. It is worth mentioning that strong conjugated aromatic system such as 1-methylbenzo[*g*]quinoxalin-2(1*H*)-one provided the desired product **3af** in a yield of 48%. We next studied the compatibility with *N*-substituted quinoxalinones with R_1 = H. To our delight, various *N*-substituted quinoxalinones were well compatible in this reaction system. We observed that *N*-protected aliphatic groups such as *N*-propyl, *N*-butyl, *N*-cyclohexylmethyl, *N*-esteryl, *N*-2-oxo-2-phenylethyl, *N*-allylic, *N*-cinnamyl and *N*-benzyl were all suitable for this reaction, providing the desired products in moderate to good yield. In addition, *N*-phenyl quinoxalinone proceeded smoothly to give the corresponding product **3ar** in 72% yield.

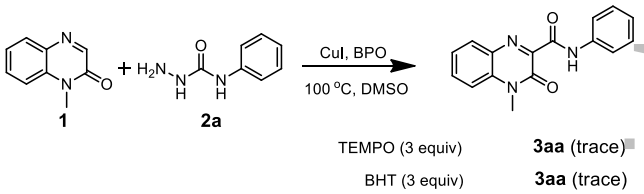
Table 3. Synthesis of the products **3ba**–**3bk**.[a],[b]



[a] Unless specifically noted otherwise, reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), CuI (0.02 mmol), BPO (0.6 mmol), solvent (1.5 mL), 100 °C, 18 h.
[b] Isolated yield.

Further, we studied the scope of carbamoylation of quinoxalin-2(1*H*)-ones reaction by investigating a wide variety of *N*-substitued hydrazinecarboxamide compounds (Table 3). The substituents (R_3) on the *N*-phenyl was first investigated. Both electon-withdrawing groups (4-Cl, 4-Br, 4-F) and electron-donating groups (4-methoxy, 4-methyl, 4-*tert*-butyl) afforded the desired compound **3ba-3bf** in good yield. When the substituent was present in *ortho*-position, the corresponding product **3bg** was obtained in 76% yield. We were pleased to see that sterically hindered amides was successfully introduced at C3 position of quinoxalin-2(1*H*)-one (**3bh**-**3bi**). In addition, *N*-aliphatic group substrate (*N*-cyclohexylhydrazinecarboxamide) proceed smoothly to give the desired compound **3bj** in 62% yield. Finally, the π-extended aromatic **2ak** provided the expected product **3bk** in 60% yield.

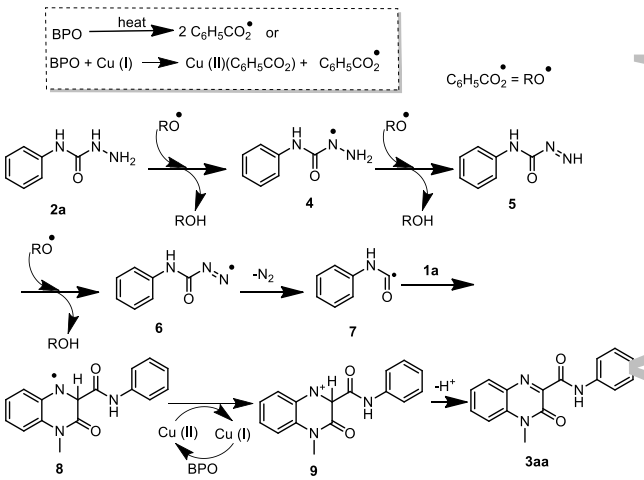
To provide further insight into the reaction system, we peformed the reaction in the presence 3 equiv. of BHT or TEMPO under the standard conditions. The transformation was completely inhibited (Scheme 2). This result indicated that the reaction may proceed via a radical pathway.



Scheme 2. Control experiments.

On the basis of the control experiments and literature reports,[11],[12],[23] we proposed a plausible reaction mechanism (Scheme 3). The benzoyl radical is generated via homolysis or copper-catalyzed decomposition of dibenzoyl peroxide. Radical intermediate **4** was generated by the single-electron transfer between *N*-phenylhydrazinecarboxamide (**2a**) and RO•. The stepwise single-electron transfer and deprotonation forms radical intermediate **7** with the release of molecular nitrogen. The addition of **7** to the **1a** affords radical intermediate **8**, which is further oxidized by Cu (II) to form nitrogen cation intermediate **9**. Finally, desired compound **3aa** is obtained by the deprotonation of **9**.

Scheme 3. Presumptive reaction mechanism.



In conclusion, an efficient and simple method for synthesis of 3-carbamoylated quinoxalin-2(1*H*)-ones base on copper-catalyzed direct carbamoylation of quinoxalin-2(1*H*)-ones at C3 position has been reported. This process exhibits good functional group tolerance with a broad substrate scope and provides an efficient method for the introduction sterically hindered amides at C3 position of quinoxalin-2(1*H*)-one. This method features cheap catalyst

and without the necessary for pre-activation of reactant. Our research also provides a novel and efficient synthetic method for the formation of amide on *α*,*β*-unsaturated compound. Our future work will extend this efficient functionalization strategy to other *α*,*β*-unsaturated bonds.

Experimental Section

General Procedure for the carbamoylation of Quinoxalin-2(1*H*)-ones

A round-bottomed flask was charged with 1-methylquinoxalin-2(1*H*)-one (**1a**) (0.2 mmol, 0.0320 g), *N*-phenylhydrazinecarboxamide (**2a**) (0.5 mmol, 0.0756 g), BPO (0.6 mmol, 0.1453 g), CuI (0.02 mmol, 0.0038 g) and DMSO (1.5 mL). Then, the mixture was stirred at 100 ^{o}C under air until the reaction was completed (monitored by TLC). The cooled reaction mixture was added with ethyl acetate (20 mL) and and saturated aqueous NaCl (20 mL), then filtered by sintered funnel**.** The remaining aqueous was extracted with ethyl acetate (20 mL×3). The combined organic layers were dried with Na_2SO_4 and evaporated under vacuum to afford the residue. The residue was purified by column chromatography (silica gel) with petroleum ether/ethyl acetate (3: 1) to obtain pure product **3aa** as a yellow solid (70% yield).

Acknowledgements

We are grateful to the National Science Foundation of China (No. 21572117), the Shandong Key Research Program (Nos. 2019JZZY021015,2019GHY112053) for their financial support. We also are grateful to the Analytical Center for Structural Constituent and Physical Property of Core Facilities Sharing Platform, Shandong University for their technology and services support.

References

[1] a) L. Shi, H. Zhou, J. Wu, X. Li, *Mini-Rev. Org. Chem*. **2015**, *12*, 96. b) A. Carta, S. Piras, G. Loriga, G. Paglietti, *Mini-Rev. Med. Chem*. **2006**, *6*, 1179. c) M. Patel, R. J. McHugh, B. C. Cordova, R. M. Klabe, S. Erickson-Viitanen, G. L. Trainor, J. D. Rodgers, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1729. d) J. Son, J. Zhu, P. Phuan, O. Cil, A. P. Teuthorn, C. K. Ku, S. Lee, A. S. Verkman, M. J. Kurth, *J. Med. Chem*. **2017**, *60*, 2401

[2] a) M. Patel, R. J. McHugh, B. C. Cordova, R. M. Klabe, S. Erickson-Viitanen, G. L. Trainor, J. D. Rodgers, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1729. b) J. Dudash, Y. Zhang, J. B. Moore, R. Look, Y. Liang, M. P. Beavers, B. R. Conway, P. J. Rybczynski, K. T. Demarest, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4790. c) J. Miyashiro, K. W. Woods, C. H. Park, X. Liu, Y. Shi, E. F. Johnson, J. J. Bouska, A. M. Olson, Y. Luo, E. H. Fry, V. L. Giranda, T. D. Penning, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 4050. d) Y. Zou, X. Qin, X. Hao, W. Zhang, S. Yang, Y. Yang, Z. Han, B. Ma, C. Zhu, *Bioorg. Med. Chem. Lett*. **2015**, *25*, 3924.

[3] a) T. Harayama, Y. Tezuka, T. Taga, F. Yoneda, *J. Chem. Soc., Perkin Trans. 1* **1987**, 75. b) J. B. Townsend, F. Shaheen, R. Liu, K. S. Lam, *J. Comb. Chem*. **2010**, *12*, 700. c) J. Unitt, M. Fagura, T. Phillips, S. King, M. Perry, A. Morley, C. MacDonald, R. Weaver, J. Christie, S. Barber, R. Mohammed, M. Paul, A. Cook, A. Baxter, *Bioorg. Med. Chem. Lett*. **2011**, *21*, 2991.

[4] J. Liu, D. Yang, X. Yang, M. Nie, G. Wu, Z. Wang, W. Li, Y. Liu, P. Gong, *Bioorg. Med. Chem*. **2017**, *25*, 4475.

[5] Q. Zhong, R. Liu, G. Liu, *Mol. Diversity* **2015**, *19*, 829.

[6] C. De Savi, R. J. Cox, D. J. Warner, A. R. Cook, M. R. Dickinson, A. McDonough, L. C. Morrill, B. Parker, G. Andrews, S. S. Young, P. S. Gilmour, R. Riley, M. S. Dearman, *J. Med. Chem*. **2014**, *57*, 4661.

[7] Y. Usuki, K. Mitomo, N. Adachi, X. Ping, K.-I. Fujita, O. Sakanaka, K. Iinuma, H. Iio, M. Taniguchi, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 2011.

[8] J. Zhou, P. Zhou, T. Zhao, Q. Ren, J. Li, *Adv. Synth. Catal*. **2019**, *361*, 5371.

[9] a) A. Gupta, M. S. Deshmukh, N. Jain, *J. Org. Chem*. **2017**, *82*, 4784. b) W. Wei, L. Wang, P. Bao, Y. Shao, H. Yue, D. Yang, X. Yang, X. Zhao, H. Wang, *Org. Lett*. **2018**, 20, 7125.

[10] J. Yuan, J. Fu, J. Yin, Z. Dong, Y. Xiao, P. Mao, L. Qu, Org. Chem. Front. 2018, 5, 2820-2828.

[11] L. Hu, J. Yuan, J. Fu, T. Zhang, L. Gao, Y. Xiao, P. Mao, L. Qu, *Eur. J. Org. Chem*. **2018**, *30*, 4113.

[12] a) K. Yin, R. Zhang, *Org. Lett*. **2017**, *19*, 1530. b) J. Yuan, S. Liu, L. Qu, *Adv. Synth. Catal*. **2017**, *359* 4197.

[13] a) J. Yuan, J. Fu, S. Liu, Y. Xiao, P. Mao, L. Qu, *Org. Biomol. Chem*. **2018**, *16*, 3203. b) X. Zeng, C. Liu, X. Wang, J. Zhang, X. Wang, Y. Hu, *Org. Biomol. Chem*. **2017**, *15*, 8929.

[14] M. Gao, Y. Li, L. Xie, R. Chauvin, X. Cui, *Chem. Commun*. **2016**, *52*, 2846.

[15] L. Wang, Y. Zhang, F. Li, X. Hao, H. Zhang, J. Zhao, *Adv. Synth. Catal*. **2018**, *360*, 3969.

[16] a) J. D. Majmudar, H. B. Hodges-Loaiza, K. Hahne, J. L. Donelson, J. Song, L. Shrestha, M. L. Harrison, C. A. Hrycyna, R. A. Gibbs, *Bioorg. Med. Chem*. **2012**, *20*, 283. b) V. Vagenende, T. Ching, R. Chua, N. Thirumoorthi, P. Gagnon, *ACS Appl. Mater. Interfaces* **2013**, *5*, 4472. c) N. A. Biok, A. D. Passow, C. Wang, C. A. Bingman, N. L. Abbott, S. H. Gellman, *Biochemistry* **2019**, *58*, 4821.

[17] a) C. E. Puerto Galvis, V. V. Kouznetsov, *J. Org. Chem*. **2019**, *84*, 15294. b) M. M. Pompeo, J. H. Cheah, M. Movassaghi, *J. Am. Chem. Soc*. **2019**, *141*, 14411. c) T. Che, Y. Wang, Z. Huang, J. Tan, Z. Huang, S. Chen, *Molecules* **2018**, *23*, 493. d) M. D. Patil, G. Grogan, H. Yun, *ChemCatChem* **2018**, *10*, 4797.

[18] a) L. Wang, Y. Zhang, F. Li, X. Hao, H. Zhang, J. Zhao, *Adv. Synth. Catal*. **2018**, *360*, 3969. b) Handoko, S. Satishkumar, N. R. Panigrahi, P. S. Arora, *J. Am. Chem. Soc*. **2019**, *141*, 15977. c) T. Nanjo, E. C. de Lucca, M. C. White, *J. Am. Chem. Soc.* **2017**, *139*, 14586. d) K. Tani, B. M. Stoltz, Nature **2006**, *441*, 731

[19] D. G. Brown, J. Bostrom, *J. Med. Chem*. **2016**, *59*, 4443.

[20] A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski, *J. Comb. Chem.* **1999**, *1*, 55.

[21] a) E. Valeur, M. Bradley, *Chem. Soc. Rev*. **2009**, *38*, 606. b) H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, *Chem. Soc. Rev*. **2014**, *43*, 2714. c) F. de Azambuja, T. N. Parac-Vogt, *ACS Catal*. **2019**, 9, 10245. d) T. Narendar Reddy, A. Beatriz, V. Jayathirtha Rao, D. Pires de Lima, *Chem. - Asian J.* **2019**, *14*, 344. e) K. Hollanders, B. U. W. Maes, S. Ballet, *Synthesis* **2019**, *51*, 2261. f) U. Dutta, A. Deb, D. W. Lupton, D. Maiti, *Chem. Commun*. **2015**, *51*, 17744. g) A. V. A. Gholap, S. Maity, C. Schulzke, D. Maiti, A. R. Kapdi, *Org. Biomol. Chem*. **2017**, *15*, 7140.

[22] a) Z. Zhang, C. Xie, X. Tan, G. Song, L. Wen, H. Gao, C. Ma, *Org. Chem. Front*. **2015**, *2*, 942. b) X. Chu, T. Duan, X. Liu, L. Feng, J. Jia, C. Ma, *Org. Biomol. Chem*. **2017**, *15*, 1606. c) H. Liu, T. Zhai, S. Ding, Y. Hou, X. Zhang, L. Feng, C. Ma, *Org. Chem. Front*. **2016**, *3*, 1096.

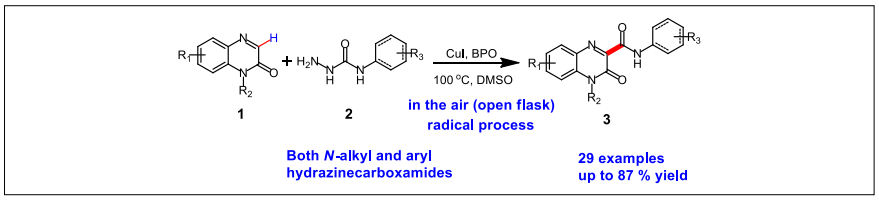
[23] a) X. Li, M. Fang, P. Hu, G. Hong, Y. Tang, X. Xu, *Adv. Synth. Catal*. **2014**, *356*, 2103. b) X. Xu, Y. Tang, X. Li, G. Hong, M. Fang, X. Du, *J. Org. Chem*. **2014**, 79, 446. c) T. Taniguchi, Y. Sugiura, H. Zaimoku, H. Ishibashi, *Angew. Chem., Int. Ed*. **2010**, *49*, 10154.

10.1002/ejoc.201901858

Entry for the Table of Contents

Copper-Catalyzed Direct Carbamoylation of Quinoxalin-2(1*H*)-Ones with Hydrazinecarboxamides under Mild Conditions

Xianglong Chu, Yujuan Wu, Haigen Lu, Bingchuan Yang* and Chen Ma*



An efficient and simple method for synthesis of 3-carbamoylated quinoxalin-2(1*H*)-ones base on copper-catalyzed direct carbamoylation of quinoxalin-2(1*H*)-ones at C3 position has been reported, This process provides a series of 3-carbamoylquinoxalin-2(1*H*)-one derivatives in moderate to good yields under mild conditions with good functional group tolerance. Our work provide a novel and efficient synthetic method for the formation of amide.

Key Topic*: Carbamoylation; Quinoxalin-2(1*H*)-ones; C-H bond activation

Institute and/or researcher Twitter usernames: ((optional))