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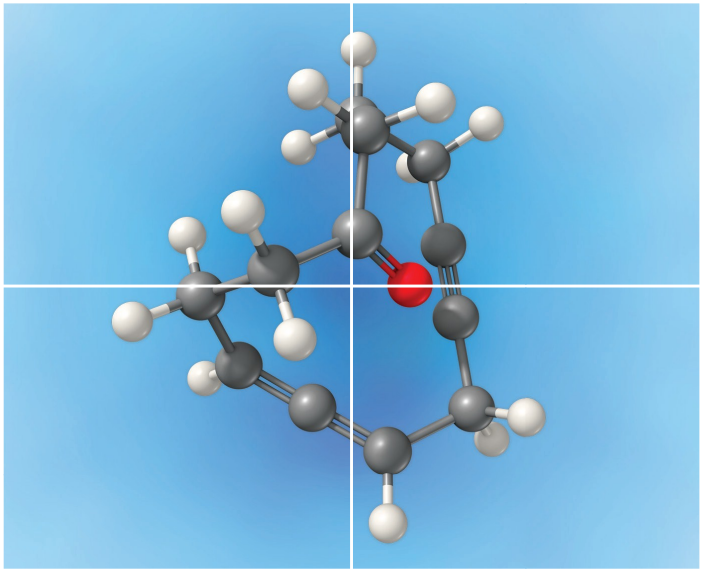

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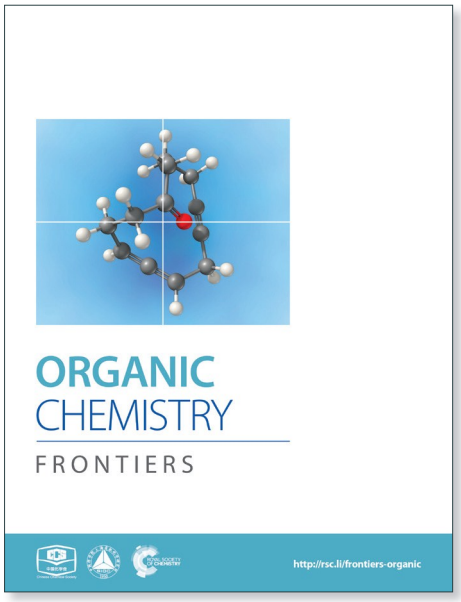

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COMMUNICATION

Copper(I) Catalyzed C(sp^2)-N bond formation: Synthesis of Pyrrolo[3,2-*c*]quinolinone Derivatives

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Zhiguo Zhang,*[a] Jingjing Qian,[a] Guisheng Zhang,*[a] Nana Ma,[a] Qingfeng Liu,[a] Tongxin Liu,[a] Kai Sun,[b] Lei Shi[a]

An intramolecular copper-catalyzed direct C(sp^2)-H activation/C(sp^2)-N bond formation reaction has been developed for the synthesis of pyrrolo[3,2-*c*]quinolinone derivatives in an oxygen atmosphere.

Natural products containing the pyrrolo[3,2-*c*]quinoline skeleton were first discovered in Martinellic acid and Martinelline in 1995.[1] These tricyclic compounds, together with other synthetic pyrrolo[3,2-*c*]quinoline derivatives, have been demonstrated to possess significant biological activity as KYN-3-Ohase inhibitors,[2] Hedgehog signaling inhibitors,[3] antitumor activity,[4] gastric (H^+/K^+)-ATPase inhibitor,[5] and others.[6] Many synthetic approaches are available for the synthesis of substituted pyrrolo[3,2-*c*]quinolines. The two most common synthetic strategies are the cyclization of functionalized quinolines[3, 7] and the aza Diels-Alder reaction of *N*-phenylmethanimines with pyrroles.[8] Beyond these specific methods, other general strategies for the construction of the tricyclic pyrroloquinoline ring system can be used, based on the Heck reaction,[9] radical cyclisation[10], and 1,3-dipolar cycloadditions.[11] However, a critical review of the literature shows that the construction of the quinolinone structural motif in pyrrolo[3,2-*c*]quinolinone derivatives has not been completed by means of C–H activation/C–N coupling reactions. We present here a facile method to prepare this type of tricycle compounds in the presence of CuI under O_2, in DMSO via the direct C(sp^2)–H activation/C(sp^2)–N coupling reactions (Figure 1).

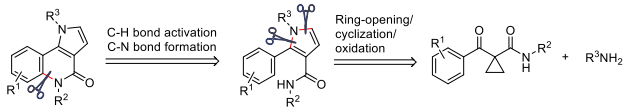


Figure 1 Retrosynthetic analysis for pyrrolo[3,2-*c*]quinolinones.

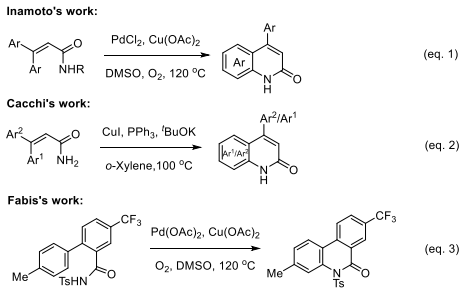
The construction of C(sp^2)-N bonds in aromatic compounds[12] is an important transformation because it provides access to nitrogen-containing molecules of great interest in synthetic, biological, medicinal, materials sciences, coordination chemistry, and natural products chemistry.[13] Metal-catalyzed C(sp^2)-N bond formation reactions have been widely used in the construction of various five-, six-, and seven-membered *N*-containing heterocycles.[14] Stoichiometric amounts of copper were first used for the construction of C(sp^2)-N bonds by Ullmann and Goldberg in 1903.[15] In the 1990s, Buchwald and Hartwig independently developed Pd- and Cu-catalyzed *N*-arylation reactions with the help of the appropriate diamine or phosphine ligands.[16] Subsequently, considerable advances have been achieved and various metal salts (such as Cu, Pd, Ni, Rh, and Fe), in catalytic amounts, have been used for these reactions in the presence of various ligands.[14a, 17] However, they often need pre-prepared activated aryl (pseudo)halides (X-Ar, X = Cl, Br, I, OTf, OTS) to react with the amine nucleophiles, which reduces the scope and efficiency of the reaction.[16c-f, 18] In comparison, the formation of C(sp^2)-N bond by direct C(sp^2)-H activation/C(sp^2)-N coupling of aromatic compounds with amines would be more practical.[17a, 17c, 19] Several groups have investigated the construction of 2-quinolinones via the intramolecular direct aromatic C(sp^2)-H activation/C(sp^2)-N bond formation reaction in the presence of metal catalysts. In 2010, Inamoto et al.[20] reported that 3,3-diarylacrylamides could be smoothly transformed into 2-quinolinone compounds in the presence of $PdCl_2$ and $Cu(OAc)_2$ under O_2 (Scheme 1, eq. 1). Soon after, Cacchi and co-works[21] reported a copper-catalyzed approach for the construction of the 2-quinolones from similar starting materials and the reaction selectively gave two products in ratio of 92:8 to 99:1 (Scheme 1, eq. 2). Recently, Fabis and co-

[a] *Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, P. R. China. E-mail: zhangzg@htu.edu.cn and zgs6668@yahoo.com*

[b] *College of Chemistry and Chemical Engineering, Anyang Normal University, Anyang 455000, P. R. China.*

† Electronic supplementary information (ESI) available: Experimental procedure, ^1H and ^{13}C NMR spectra of all compounds. CCDC 1056410, 1057211, 1056498-1056499, 1056576-1056577. For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/x0xx00000x

workers[17b] focused on *N*-tosylcarboxamide as a transformable directing group for the Pd-catalyzed C(sp^2)-H ortho-arylation reaction of *N*-tosylbenzamides with iodotoluenes, in which the intramolecular cyclization product 3-methyl-5-tosyl-8-(trifluoromethyl)phenanthridine-6(5*H*)-one was obtained as a special case in the synthesis of biarylcarboxamides (Scheme 1, eq. 3).

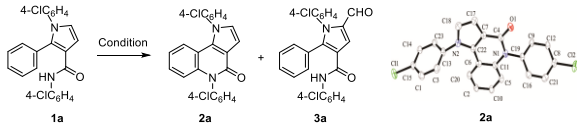


Scheme 1 Metal-catalyzed the construction of the 2-quinolones skeleton.

Very recently, we developed a facile ring-opening/cyclization/dehydrogenation domino reaction for the construction of multiple-substituted pyrroles by the reactions of doubly activated cyclopropanes with anilines in the presence of an iron salt.[22] We have also found a series of derivatization reactions to form multi-substituted pyrroles.[23] We are interested in the further derivatization of readily available pyrroles for the construction of pyrrolo[3,2-*c*]quinolinones. We reasoned that the desired fused tricyclic pyrrolo[3,2-*c*]quinolinones could be synthesized via a metal-catalyzed intramolecular annulation by using the starting material of 2-aryl-1*H*-pyrrole-3-carboxamides (Figure 1). Many more hetero-fused quinoline derivatives would be available through this route. Initially, compound **1a** was selected as the model substrate to explore the optimal conditions for the ring-closure reaction. After many attempts, it was found that pyrrolo[3,2-*c*]quinolin-4-one (**2a**) could be obtained in 69% yield in the presence of 5 mol% CuI at 160 °C after 9 h (Table 1, entry 1). The structure of **2a** was further confirmed by single-crystal X-ray diffraction analysis (Table 1).[24] The yield of **2a** decreased significantly if the temperature decreased (Table 1, entries 2 and 3). Further experiments showed that the yield of **2a** could not be increased by increasing the amount of CuI (Table 1, entries 4 and 5). When performed under N_2, the reaction did not afford the desired compound **2a** and most of the starting material **1a** was recovered, which indicated that the dioxygen was involved in the reaction (Table 1, entry 6). Other copper salts including $Cu(OAc)_2$, $Cu(acac)_2$, CuBr (Table 1, entries 7–9), and Cu powder were proved to be less effective than CuI, especially for the $Cu(OAc)_2$ and $Cu(acac)_2$ catalysts, as they selectively gave the 2-formylpyrrole derivative **3a** in 32% and 58% yield, respectively. CuCl and Cu_2O showed a similar catalytic effect to CuI, but they needed longer reaction times (Table 1, entries 10 and 11). Other high boiling solvents such as DMF and xylene were proved to be inefficient (Table 1, entries 13 and 14).

With the optimized conditions in hand (Table 1, entry 1), we

Table 1 Survey of the reaction conditions[a]



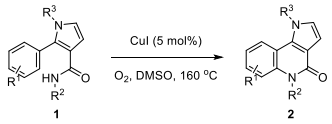
Entry	Cat. (equiv)	Solvent	Temp/°C	Time/h	Yield/%
1	CuI (0.05)	DMSO	160	9	69[b]
2	CuI (0.05)	DMSO	150	9	9[c]
3	CuI (0.05)	DMSO	130	36	35[d]
4	CuI (0.2)	DMSO	160	11	56%
5	CuI (0.5)	DMSO	160	11	58%
6	CuI (0.05)	DMSO	160	41	0[e]
7	$Cu(OAc)_2$ (0.05)	DMSO	160	4	25[f]
8	$Cu(acac)_2$ (0.05)	DMSO	160	37	0[g]
9	CuBr (0.05)	DMSO	160	11	50[h]
10	CuCl (0.05)	DMSO	160	16	72
11	Cu_2O (0.05)	DMSO	160	28	75
12	Cu (0.05)	DMSO	160	18	53
13	CuI (0.05)	DMF	160	33	25[i]
14	CuI (0.05)	Xylene	Reflux	12	0[j]

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.2 mmol), CuI (0.05 equiv) in DMSO (1.5 mL) at 160 °C under O_2 (balloon, 1 atm). [b] The yield is an average of four reactions and less than 10% of **3a** was isolated in each of the four reactions. [c] 88% of **1a** was recovered. [d] 50% of **1a** was recovered. [e] Reaction was performed under N_2 and 92% of **1a** was recovered. [f] 32% of **3a** was obtained. [g] 58% of **3a** was obtained. [h] 18% of **3a** was obtained. [i] 65% of **1a** was recovered. [j] 95% of **1a** was recovered.

proceeded to explore the scope and limitations of this ring-closure reaction using various starting materials **1**. The results are summarized in Table 2. The substituents at the amide moiety were investigated first. It was found that the reactions of **1a–h** bearing an aryl on the nitrogen afforded the corresponding pyrrolo[3,2-*c*]quinolinones **2a–h** in 46-70% yields, and that the electronic nature (i.e., electron-donating or electron-withdrawing) and the position (i.e., *ortho*-, *meta*-, or *para*-position) of the substituents (e.g., -OMe, -Cl and $-CO_2Et$) on the phenyl ring had little impact on the yields. However, benzyl and tertiary butyl alkyl groups on the nitrogen only gave the 2-formylpyrroles **3i** in 70% and **3j** in 40% yield, respectively, instead of the desired ring-closure products **2i** and **2j**. The effect of the substituent on the nitrogen of pyrrole ring moiety was also examined. These experiments demonstrated that the yields of **2k** (73%) and **2m** (73%) with *p*-CO_2Et phenyl and *p*-OMe phenyl substituents were slightly higher than **2l** with a phenyl group on the nitrogen. The substrate **1n** with a benzyl on the nitrogen gave **2n** in 50% yield. However, *tert*-butyl substituted substrate **1o** did not give the desired compound **2o** and most of **1o** was recovered. In addition, variations of the aryl at the α-position of the pyrrole ring were also taken into account. It seemed that the position of the substituent had a significant effect on the yield of **2**. The substrates **1p**, **1q** and **1t** with the -OMe and -Cl substituents at the *para*-position of the aryl provided the products **2p** (65%), **2q** (71%) and **2t** (67%) in approximately equal yields. In contrast, compounds **1r**, **1s**, and **1u** with the -OMe or -Cl substituent at the *ortho*- or *meta*-position, mainly produced 2-

formylation products **3r**, **3s**, and **3u** along with an unidentified complex mixture of additional products. The product of the cyclization of **1r** gave the target compound **2r** regiospecifically with the *para*-position of the methoxyl group, in 23% yield.

Table 2 Extension of the reaction scope[a]

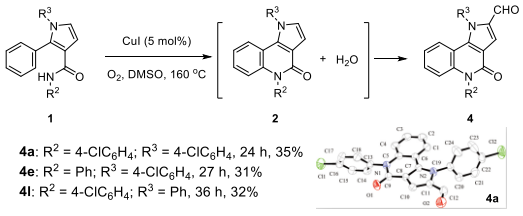


1 2

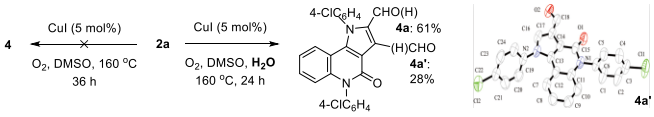
Compound	R^1	R^2	R^3	Time/h	Yield/%
2a	H	4-ClC_6H_4	4-ClC_6H_4	9	69
2b	H	3-ClC_6H_4	4-ClC_6H_4	11	61
2c	H	2-ClC_6H_4	4-ClC_6H_4	10	60
2d	H	4-$CO_2EtC_6H_4$	4-ClC_6H_4	12	63
2e	H	Ph	4-ClC_6H_4	12	46
2f	H	4-$MeOC_6H_4$	4-ClC_6H_4	12	70
2g	H	3-$MeOC_6H_4$	4-ClC_6H_4	9	65
2h	H	2-$MeOC_6H_4$	4-ClC_6H_4	8	53
2i	H	Bn	4-ClC_6H_4	10	0[b]
2j	H	^{t}Bu	4-ClC_6H_4	15	0[c]
2k	H	4-ClC_6H_4	4-$CO_2EtC_6H_4$	18	73
2l	H	4-ClC_6H_4	Ph	12	52
2m	H	4-ClC_6H_4	2-$MeOC_6H_4$	9	73
2n	H	4-ClC_6H_4	Bn	8	50
2o	H	4-ClC_6H_4	^{t}Bu	20	0[d]
2p	4-MeO	4-ClC_6H_4	Ph	38	65
2q	4-MeO	4-ClC_6H_4	4-ClC_6H_4	10	71[e]
2r	3-MeO	Ph	4-ClC_6H_4	11	23[f]
2s	2-MeO	Ph	4-ClC_6H_4	31	0[g]
2t	4-Cl	Ph	4-ClC_6H_4	20	67
2u	3-Cl	Ph	4-ClC_6H_4	11	0[h]

[a] Unless otherwise indicated, all reactions were carried out with **1** (0.2 mmol), CuI (0.05 equiv) in DMSO (1.5 mL) at 160 °C under O_2 (balloon, 1 atm) and stopped when all of **1** had disappeared, and they produced less than 10% of the by-products **3**. [b] 70% of **3i** was obtained. [c] 40% **3j** of was obtained. [d] 86% of **1o** was recovered. [e] 14% of **3q** was obtained. [f] The structure was determined by X-ray crystallography and 61% of **3r** was obtained. [g] 68% of **3s** was obtained. [h] 62% of **3u** was obtained.

In these transformations, a trace amount of by-products **4** were observed, and **4a** was isolated and characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and a single-crystal X-ray diffraction analysis (Scheme 2). Interestingly, the products **2** would gradually disappear to form **4** when the reaction times were prolonged, which would give a direct method to produce valuable α-formyl pyrrolo[3,2-*c*]quinolinones **4** from pyrroles **1**. As examples, three randomly selected reactions with starting materials **1** afforded the desired compounds **4a**, **4e**, and **4l** in 31–35% yields when the reactions were prolonged until the intermediates **2** had disappeared. Although the yields were moderate, these preliminary results are meaningful given the advantages of the one-pot tandem reactions.

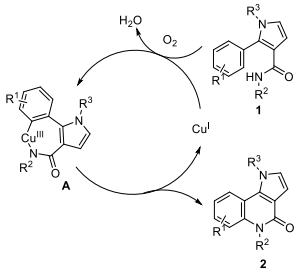


Scheme 2 Examples of one-pot cascade reactions of **1** to α-formyl pyrrolo[3,2-*c*]quinolinones 4



Scheme 3 α- And β-formylation reaction of **2a**.

During the transformation of **1a** to **4a**, it was observed that compound **2a** was the single product early in the reaction (6 h), and later the formylated pyrrole **3a** formed more gradually, and finally the α-formyl pyrrolo[3,2-*c*]quinolinone **4a** along with an un-isolated mixture (mainly consisting of **3a** and the β-formyl pyrrolo[3,2-*c*]quinolinone **4a'**) were produced at the end (24 h). This observation indicates that the water formed *in situ* is necessary for the formylation, which draws a carbon from a solvent DMSO.[23a, 23b] This was further confirmed by the reactions of pure **2a** (Scheme 3). The reaction did not occur under the standard conditions; however, it afforded the formylated isomers **4a** (R_f = 0.25, petroleum ether/EtOAc 2:1, 61%) and **4a'** (R_f = 0.50, petroleum ether/EtOAc 2:1, 28%), as characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and by single-crystal X-ray diffraction analysis, when 10 equiv. water was added to the reaction mixture. The preliminary study revealed the feasibility of further modifying the target compounds **2** with an active aldehyde group.



Scheme 4 Proposed mechanism.

To clarify the reaction mechanism, three separate reactions were conducted by stoichiometric addition of an electron-transfer scavenger (1,4-dinitrobenzene), a radical clock (diallyl ether), and a radical inhibitor (hydroquinone).[25] It was observed that the reaction still proceeded smoothly to afford the desired product **2a** along with **3a**. These observed results suggest that a radical process is not involved in this transformation. In addition, control experiments showed that CuI and $Cu(OAc)_2$ could catalyze the transformation under O_2 (Table 1, entries 1 and 7), but no product was detected under N_2 (Table 1, entry 6). These results suggest that a Cu(III) species might be involved in this transformation. On the basis of these control experiments and previous literature,[17b, 20-21, 25a, 26] a plausible pathway for this pyrrolo[3,2-*c*]quinolinone

synthesis is outlined in Scheme 4. Initially, a reactive Cu(III) intermediate **A** is formed by the reaction of Cu(I) and substrate **1** and O_2 *in situ*[27] via an electrophilic metallation or a C–H bond activation.[28] Reductive elimination delivers the product **2** with concurrent formation of Cu(I). Formylation products **3** and **4** are generated via the aerobic Cu(I)-catalyzed Pummerer-like reaction,[29] and DMSO serving as the one carbon donor for the -CHO.[23a, 23b, 30]

Conclusions

In summary, we have described the direct C(sp^2)-H functionalization and intramolecular amide arylation for the efficient construction of substituted pyrrolo[3,2-*c*]quinolinones. The method provides an alternative, novel, efficient, and valuable route to the pyrrolo[3,2-*c*]quinolinones. Preliminary investigations on the preparation of valuable formylated pyrrolo[3,2-*c*]quinolinones via this method have also been carried out. Further studies of the application of the Cu(I)-catalyzed intramolecular C(sp^2)-H amination process to the synthesis of other nitrogen atom-based heterocycles are currently underway.

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