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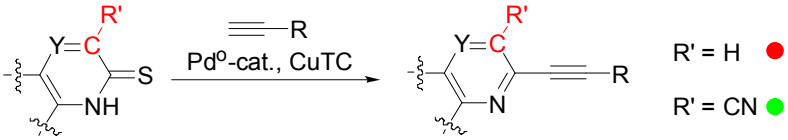

27 examples
Yields: up to 93 %

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/advances

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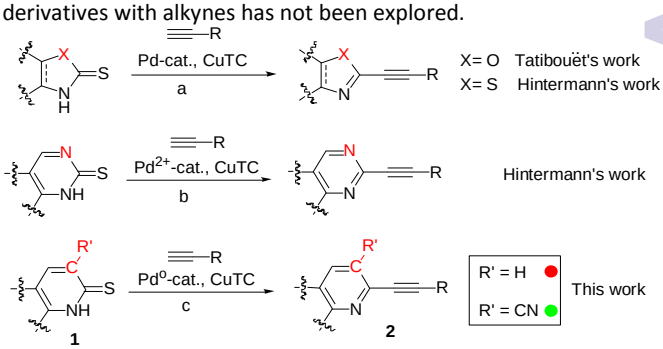
A Pd-catalyzed Cu-mediated desulfurative Sonogashira cross-coupling reaction of thioamide-type quinolone derivatives was proposed for the construction of C_{sp}^2–C_{sp} bonds. Alkynylated quinoline derivatives can be easily synthesized in moderate to excellent yields. The mechanism and effect of the 3-cyano on the reaction were also discussed.

Transition metal-catalyzed Sonogashira reaction for the formation of C_{sp}^2–C_{sp} bond is an indispensible tool for targeted and parallel synthesis of heterocyclic compounds.[1] Traditionally, all of these cross-coupling reactions employ aryl halides, aryl triflates, aryl tosylates and aryl sulfonates as electrophilic coupling partners to perform the cross-coupling with nucleophilic organometallic reagents to produce new C–C bonds. However, the limited stability and/or accessibility of the corresponding heteroaromatic derivatives is somewhat problematic.

In 2000, Liebeskind and Srogl reported a new efficient Pd-catalyzed cross-coupling reaction of thiol ester and thioether species.[2] Later, Kappe and co-workers demonstrated that the use of non-basic Liebeskind–Srogl conditions was not only applicable to thiol esters and thioethers as substrates, but could also be extended to latent free thiol group-containing substrates including pyrimidinethiones[3] and cyclic thio-amides[4]. Considering the wide distribution of C–S bonds in natural products, pesticides and drugs, their transformation via metal-catalyzed coupling reaction have become more and more important in organic chemistry.[5]

Van der Eycken and co-workers reported an unprecedented microwave-assisted desulfurative Sonogashira cross-coupling protocol for the alkynylation of the C-3 of phenylsulfanylated-2(1*H*)-pyrazinones.[6] It was demonstrated for the first time that the cleavage of C-S from the resin without prior oxidation of the sulfur linker can be realized with the Sonogashira alkynylation of C–S with alkynes in the presence of aryl chloride. The scope of this novel reaction was then extended to pyrimidine functionalized-disulfides.[7]

Encouraged by Kappe's work, Tatibouët reported the desulfurative alkynylations of 1,3-oxazolidine-2-thiones (OZTs) and 1,3-oxazoline-2-thiones (OXTs) with bases (Scheme 1a, X = O).[8] This method was also used in the total synthesis of natural products with anti-tumor activity.[9] Hintermann reported a base-free reaction system for the coupling reactions of 2-mercapto-1,3-pyrimidine and alkynes (Scheme 1b), and this method was scoped to 1,3-thiazoline-2-thiones (Scheme 1a, X = S).[10] However, the succeeded Sonogashira reactions were only used to substrates of which the latent free thiol functionality linked next to two heteroatoms (marked with red in Scheme 1), such as O, S and N. To the best of our knowledge, Sonogashira coupling reaction of thioamide-type quinolone derivatives with alkynes has not been explored.



Scheme 1. Desulfurative Sonogashira cross-coupling reactions

Considering the limitation of the scope of the substrates, we inferred that the coordination of the heteroatoms on the substrates, such as oxaline, thiazoline and pyrimidine, to the Pd(0) catalyst could stabilize the Pd(0)-substrate complex to facilitate the oxidative addition procedure, therefore making the cross-coupled products easier to be produced. To simply testify the supposition, we employed 2-mercaptoquinoline (R' = H, Scheme 1c), which could not provide a heteroatom to coordinate to the Pd(0) catalyst, as the substrate to perform the desulfurative Sonogashira reaction with phenylacetylene. As expected, it failed to afford the desired alkynylated product. In 2011, Sun and co-workers reported a C–H bond activation protocol using cyano as a directing group.[11] A mechanism of the stabilizing effect of the coordination between the

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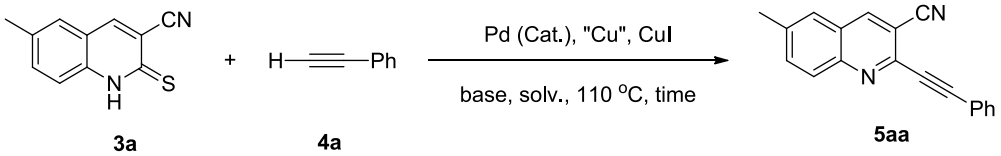
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

π-electrons of the cyano group and the Pd(0) species was proposed. Inspired by this work, we designed a 3-cyano-substituted substrate to attempt the desulfurative Sonogashira cross-coupling reaction. To our delight, the desired coupling product was isolated in good yield when 3-cyano-6-methyl-2-mercaptoquinoline **3a** was used as the substrate. As a continuing study of the desulfurative Sonogashira cross-coupling reaction, in the present work, we presented a Pd-catalyzed Sonogashira cross-coupling reaction of 3-CN assisted thioamide-type quinolone derivatives with alkynes (Scheme 1c, R'= CN).

At the beginning of our study, we chose the desulfurative coupling of 3-cyano-6-methyl-2-mercaptoquinoline **3a** with phenylacetylene **4a** in the presence of the Pd catalyst, Cu additive, CuI and base as a model system to optimize the reaction condition. As shown in Table 1, no reaction occurred without the Pd catalyst (Table 1, entry 1). Among all Pd catalysts including $Pd(PPh_3)_2Cl_2$, $Pd(MeCN)_2Cl_2$, $Pd(dba)_2$, $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$, $Pd(PPh_3)_4$ gave the highest yield under same conditions (Table 1, entries 2–8). No desired product was obtained without the Cu additive, indicating it was essential for the reaction (Table 1, entry 10). CuTC is the optimal Cu additive for this transformation, which gave the expected product in 68% yield (Table 1, entry 9). Reducing the amount of CuI from 1 equiv. to 0.5 equiv. resulted in the same yield. However, a considerable decline of the yield was observed in the absence of CuI, indicating that appropriate amount CuI was necessary for the reaction (Table 1, entries 9, 11 and 12). No desired products were obtained without base and only trace product was obtained without solvent, indicating that they were necessary for the reaction and could significantly affect the reaction (Table 1, entries 18 and 23). Among the bases tested, including Et_3N, pyridine, *N*,*N*,*N*',*N*'-tetramethylguanidine (TMG), K_2CO_3, Cs_2CO_3 and NaOH, Et_3N gave the highest yield (Table 1, entries 11 and 13–17). Among all the solvents tested, including THF, DMF, MeCN, CH_2Cl_2 and dioxane, dioxane gave the highest yield (Table 1, entries 11 and 19–22). The screening of the reaction time indicates that 15 h reaction time is the most suitable to afford the highest yield of product **5aa**. A highest yield of 75% was obtained under the optimized conditions as shown (Table 1, entry 26).

Table 1. Optimization of reaction conditions[a]



3a **4a** **5aa**

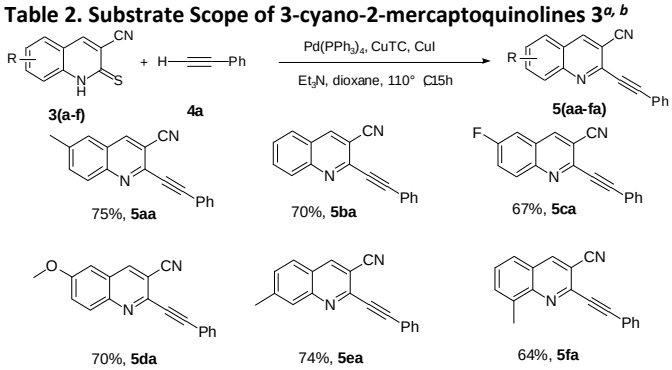
Entry	Pd (Cat.)	"Cu" (1 equiv.)	CuI	Base[b]	Solv.	time(h)	yield(%)[c]
1	-	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	0
2	$Pd(PPh_3)_2Cl_2$	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	48
3	$Pd(MeCN)_2Cl_2$	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	28
4	$Pd(dba)_2$	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	41
5	$PdCl_2$	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	24
6	$Pd(OAc)_2$	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	57
7	$Pd_2(dba)_3$	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	30
8	$Pd(PPh_3)_4$	$Cu(OTf)_2$	1 equiv.	Et_3N	THF	20	64
9	$Pd(PPh_3)_4$	CuTc	1 equiv.	Et_3N	THF	20	68
10	$Pd(PPh_3)_4$	-	1 equiv.	Et_3N	THF	20	0
11	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	THF	20	68
12	$Pd(PPh_3)_4$	CuTc	-	Et_3N	THF	20	50
13	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	pyridine	THF	20	0
14	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	TMG	THF	20	0
15	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	K_2CO_3	THF	20	11
16	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Cs_2CO_3	THF	20	60
17	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	NaOH	THF	20	trace
18	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	-	THF	20	0
19	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	DMF	20	14
20	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	MeCN	20	17
21	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	CH_2Cl_2	20	6
22	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	dioxane	20	70
23	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	-	20	trace
24	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	dioxane	5	68
25	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	dioxane	10	70
26	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	dioxane	15	75

27	$Pd(PPh_3)_4$	CuTc	0.5 equiv.	Et_3N	dioxane	48	41

[a]Conditions: **3a** (0.5 mmol), **4a** (3 equiv.), Pd (Cat.) (0.05 equiv.), "Cu" (1 equiv.), CuI, base (3 mL) and Solv. (3 mL) were mixed and heated at 110 °C under argon atmosphere.
[b]Amount of base: TMG (2.5 equiv.), K_2CO_3 (2.5 equiv.), Cs_2CO_3 (2.5 equiv.) and NaOH (2.5 equiv.).
[c]Isolated yields.

The substrate scope of thioamide-type quinolones **3** was then examined under the optimized conditions (Table 2). It is clear that a variety of 3-cyano-2-mercaptoquinolines **3** derivatives can be converted to the desired desulfurative coupling products **5aa–5fa** in good yields ranging from 64% to 75%. The reaction can also tolerate well to electron-donating groups such as methyl (**5aa, 5ea, 5fa**) and methoxy (**5da**) and electron-withdrawing groups such as fluorine (**5ca**).

Table 2. Substrate Scope of 3-cyano-2-mercaptoquinolines 3[a, b]

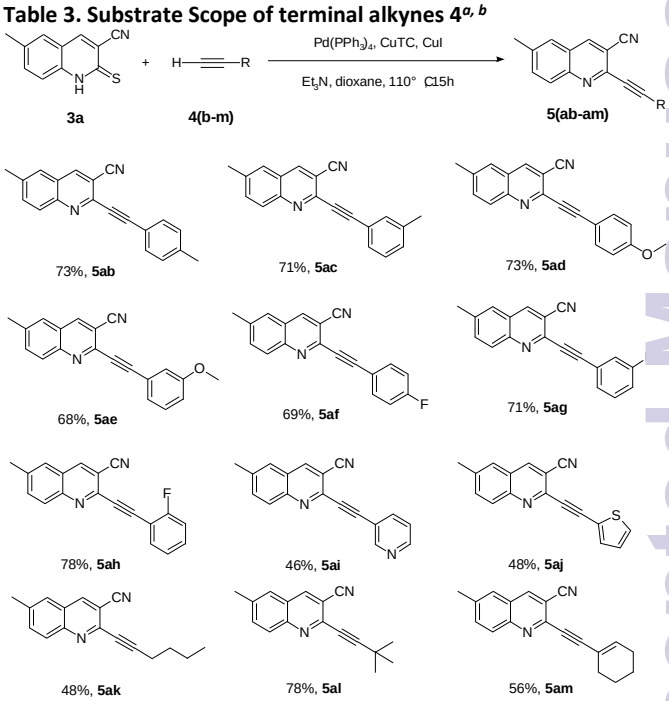


[a]Conditions: **3** (0.5 mmol), **4a** (3 equiv.), $Pd(PPh_3)_4$ (5 mol%), CuTC (1 equiv.), CuI (0.5 equiv.), Et_3N (3 mL) and dioxane (3 mL) were mixed and heated at 110 °C under argon atmosphere for 15h.
[b]Isolated yields.

Next, reactions of **3a** with various aromatic and aliphatic terminal alkynes were investigated. As shown in Table 3, the reactions with both electron-rich (**4b–4e**) and electron-poor (**4f–4h**) aromatic terminal alkynes afforded the corresponding products **5ab–5ah** in good yields ranging from 68% to 78%. The reaction with the heteroaryl alkynes afforded the desired products **5ai** and **5aj** in moderate 46% and 48% yields, respectively. The reactions with aliphatic alkynes **4k** and **4m** gave the desulfurative coupling products **5ak** and **5am** in moderate yields of 48% and 56%, respectively, while that with **4l** generated the desired product **5al** in good yield 78%, possibly due to the steric effect caused by hindering the addition of electrophiles to the C–C triple bond of the product.[10, 12]

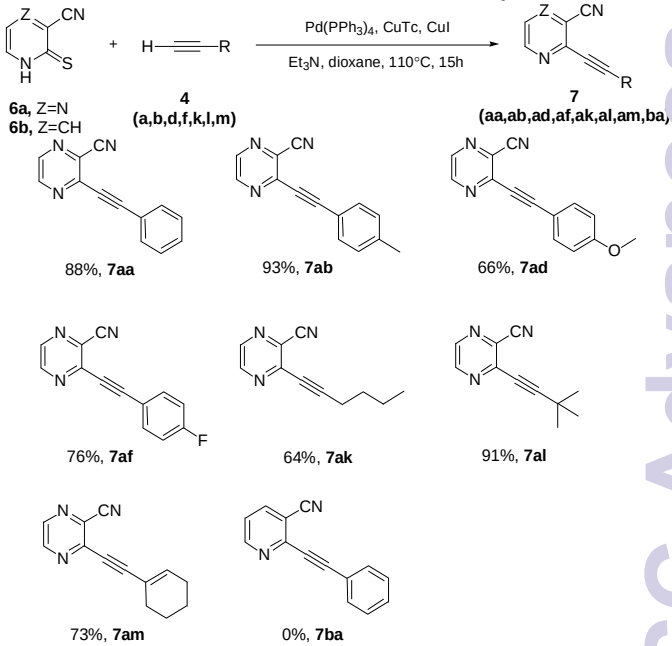
The focus of the study was then shifted to screening other substrates applicable to this method that could afford the desired products in higher yields. The reactions of 2-mercapto-3-pyrazine carbonitrile **6a** with alkynes occurred highly efficiently (Table 4). The reactions of **6a** with electron-rich and electron-poor aryl terminal alkynes produced the desired products in good to excellent yields ranging from 66% to 93% (Table 4, **7aa**, **7ab**, **7ad** and **7af**). In addition, the reactions with aliphatic terminal alkynes gave the corresponding products in good to excellent yields ranging from 64% to 91% (Table 4, **7ak**, **7al** and **7am**). The disparity among the yields of **7ak**, **7al** and **7am** once again suggests the significant influence of steric hindrance on the yields of the products. Unexpectedly, the reaction of 3-cyano-2-mercaptopyridine **6b** failed to afford the desired product **7ba**.

Table 3. Substrate Scope of terminal alkynes 4[a, b]



[a]Conditions: **3a** (0.5 mmol), **4** (3 equiv.), $Pd(PPh_3)_4$ (5 mol%), CuTC (1 equiv.), CuI (0.5 equiv.), Et_3N (3 mL) and dioxane (3 mL) were mixed and heated at 110 °C under argon atmosphere for 15h.
[b]Isolated yields.

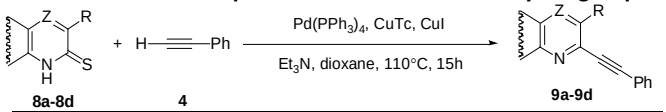
Table 4. Reaction of 6a with different terminal alkynes 4[a,b]



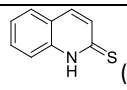
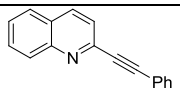
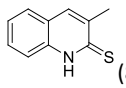
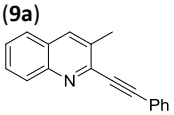
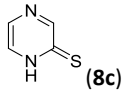
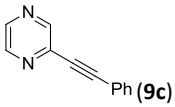
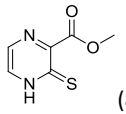
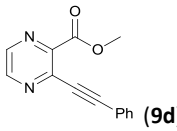
[a]Conditions: **6a** (0.5 mmol), **4** (3 equiv.), $Pd(PPh_3)_4$ (5 mol%), CuTC (1 equiv.), CuI (0.5 equiv.), Et_3N (3 mL) and dioxane (3 mL) were mixed and heated at 110 °C under argon atmosphere for 15h.
[b]Isolated yields.

The significant difference between the results of 2-mercaptoquinoline and 3-cyano-2-mercaptoquinolines **3** was evidence that the cyano group crucially facilitated the reaction. Furthermore, a series of experiments were conducted to further verify the effect of the 3-cyano group on the reaction. As mentioned above, the cross-coupling of 3-cyano-2-mercaptoquinoline **3b** with phenylacetylene **4a** produced the corresponding desulfurative Sonogashira product **5ba** in 70% yield (Table 2), while the reaction of 2-mercaptoquinoline **8a** with **4a**, as shown in Table 5, failed to afford the desired product under the same conditions (Table 5, entry 1). The desired product **9b** was isolated in a considerably lower yield of 16% with 3-methyl-2-mercaptoquinoline **8b** instead as the substrate (Table 5, entry 2). Likewise, the reaction of 2-mercaptopyrazine **8c** afforded the desired product **9c** in 20% yield (Table 5, entry 3). However, the reaction of 3-cyano-2-mercaptopyrazine **6a** produced the corresponding product **7aa** in a significantly higher yield of 88% (Table 4). It was worth mentioning that no desired product was isolated with methyl 3-mercapto-2-pyrazine-2-carboxylate **8d** as the substrate. Since the ester group was an electron-withdrawing group, similar to cyano group, it could be inferred that it was the stabilizing coordination effect of the 3-cyano group, other than electron-withdrawing effect, that crucially facilitated the desulfurative Sonogashira cross-coupling reaction.

Table 5. Verification experiments of the effect of 3-cyano group.[a]

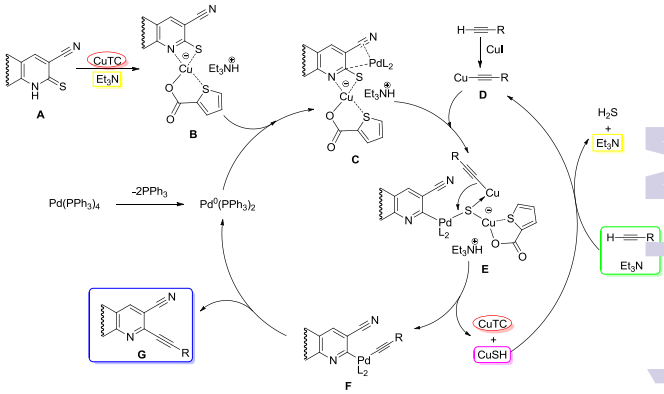


8a-8d 4 9a-9d

Entry	Substrates **8**	Products **9**	Yields (%)[b]
1	 (**8a**)	 (**9a**)	0
2	 (**8b**)	 (**9b**)	16
3	 (**8c**)	 (**9c**)	20
4	 (**8d**)	 (**9d**)	0

[a]Conditions: **8** (0.5 mmol), **4a** (3 equiv.), $Pd(PPh_3)_4$ (5 mol%), CuTC (1 equiv.), CuI (0.5 equiv.), Et_3N (3 mL) and dioxane (3 mL) were heated at 110 °C under argon atmosphere for 15h.
[b]Isolated yields.

Based on the mechanism previously reported[4] and the discussion above, we proposed a possible mechanism of the critical effect of the 3-cyano group on the reaction (Scheme 2). In the proposed mechanism we highlight the effect of 3-cyano group in transition state **C**. To a great extent, the reaction undergoes the traditional Liebeskind-Srogl catalytic recycle. Once transition state **B**[8, 12] is formed, the activated Pd(0) species coordinates both to the π-electrons of the triple bond of the cyano group and the pyridine ring to produce a stable transition state **C**,[11, 13, 14] making the oxidative addition of the C-S bond to Pd(0) much easier. This step significantly facilitates the reaction. The transmetalation of **C** and **D** leads to the formation of transition state **F**.[8, 12] The final product **G** is afforded by the reductive elimination of Pd, and the Pd(0) species returns to the catalytic recycle.



Scheme 2. Proposed reaction mechanism

Conclusions

In summary, we have successfully achieved an efficient 3-cyano assisted desulfurative Sonogashira cross-coupling reaction of thioamide-type quinolone derivatives with $Pd(PPh_3)_4$ as the catalyst, readily accessible CuTC and CuI as the additives and cheap Et_3N as base. This method can be simply conducted and provide corresponding desulfurative Sonogashira cross-coupling products in moderate to excellent yields. A variety of electron-donating and electron-withdrawing substituent groups are well tolerated. Furthermore, the significant effect of the 3-cyano group, attached next to the thioamide fragment of the substrates, on the C_{sp^2}–C_{sp} formation was investigated. Further work on detailed mechanism and extending the application of this method is ongoing in our lab.

Acknowledgements

The project is supported by the funds of National Natural Science Foundation of China (NSFC 21272009). We thank Professor Ning Jiao (Peking University) for his review and comments.

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