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Copper-promoted direct sulfenylation of C1–H bonds in 4-aryl pyrrolo[1,2-*a*]quinoxalines†

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Methods for direct functionalization of C(sp^2)–H bonds in pyrrolo[1,2-*a*]quinoxalines have witnessed emerging development over the last decade. Herein we report a new tactic to afford a selective sulfenylation of 4-aryl pyrrolo[1,2-*a*]quinoxalines with diaryl disulfides. The reactions proceeded in the presence of a copper catalyst and potassium iodide promoter. Functionalities including nitro, ester, amide, methylthio, and halogen groups were all tolerated. Our method offers a convenient route to obtain highly substituted pyrrolo[1,2-*a*]quinoxalines-based thioethers in moderate to good yields.

Pyrrolo[1,2-*a*]quinoxalines are important motifs ubiquitously found in medicinally relevant molecules or functional materials.[1] Recent studies feature new methods to develop the library of substituted pyrrolo[1,2-*a*]quinoxalines, which were traditionally limited to Pictet–Spengler-type annulation products.[2] Perhaps intangible benefits such as convenient diversification and short synthesis would be considered should direct functionalization of C–H bonds in pyrrolo[1,2-*a*]quinoxalines be successful. Thus far, methods to forge new carbon–carbon and carbon-heteroatom bonds in pyrrolo[1,2-*a*]quinoxalines have been reported.[3] One of the earliest examples presented a C1–thiocyanation and selenocyanation of pyrrolo[1,2-*a*]quinoxaline C–H bonds.[3a] Until now, the functionalization of C1–H bonds has been extensively studied, except one example for C3–H iodination.[3c] Mechanistically, high selectivity toward C1–H bonds was obtained following the electrophilic substitution. Given that certain successes are achieved, more examples are still expected with respect to better practicality and more general scope of substrates.

Carbon–sulfur bonds are often found in synthetically and practically useful molecules.[4] While the cross coupling of (pseudo)halides and thiols to afford C–S bonds has been precedented, it suffers from inevitable pre-functionalization. Thus, sulfenylation of C–H bonds would be beneficial from the atom- and step-economy standpoints.[5] Following our continuing interest,[3d] herein we develop a method to afford thioethers *via* the direct sulfenylation of C1–H bonds in pyrrolo[1,2-*a*]quinoxalines with diaryl disulfides. In comparison to thiophenols, diaryl disulfides would offer advantages including odorless and easily handling solids. Activation of S–S bonds to afford radical or electrophilic sulfur-containing adducts could be feasibly obtained in the presence of cheap and commercial iodide sources.[6] As such, we hypothesized that electrophilic sulfenylation of C1–H bonds in pyrrolo[1,2-*a*]quinoxalines is possible should disulfides be combined with suitable iodide and oxidant. It should be noted that the thioethers reported in our study are possibly obtained using a previously developed method,[3a] albeit in a lengthy sequence of hydrolysis and cross coupling.

We started our investigation by studying the reaction of 4-phenyl pyrrolo[1,2-*a*]quinoxaline **1a** and diphenyl disulfide **2a** (Table 1). The product **3aa** was obtained in 73% isolated yield using $CuCl_2$ catalyst, KI promoter, DMSO solvent, under air, at 120 °C (entry 1).[7] The regioselectivity was confirmed by comparing the coupling constant of protons on C2 and C3 with those previously reported regarding the C1–H functionalization.[3a,h] The reaction was easy to scale up, as 70% yield of **3aa** was isolated in a 5 mmol scale run. Omitting $CuCl_2$ gave an

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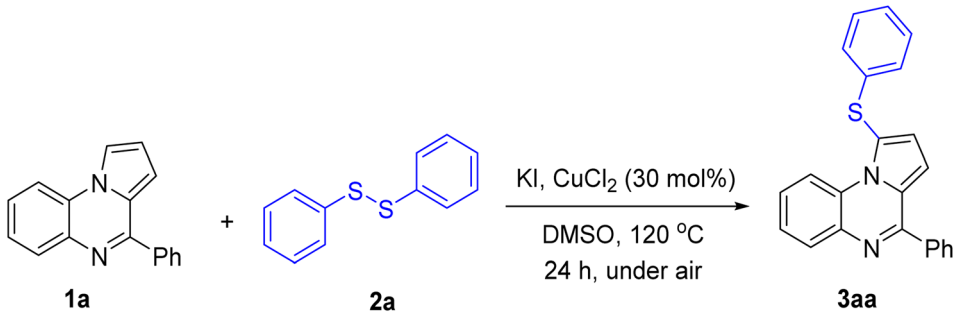
Table 1 Study of reaction conditions[a]



Entry	Variation from standard conditions	Yield of **3aa** (%)
1	None	73, 70[b]
2	Without $CuCl_2$	<10
3	CuI instead of $CuCl_2$	38
4	$Cu(OAc)_2$ instead of $CuCl_2$	27
5	$CuBr_2$ instead of $CuCl_2$	53
6	$FeCl_3$ instead of $CuCl_2$	55
7	nBu$_4$NI instead of KI	72
8	NaI instead of KI	64
9	I_2 instead of KI	45
10	Without KI	<10
11	Under argon	60
12	DMF instead of DMSO	25
13	1,4-Dioxane instead of DMSO	30
14	Toluene instead of DMSO	31

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.05 mmol), $CuCl_2$ (0.03 mmol), KI (0.05 mmol), DMSO (1 mL), 120 °C, 24 h, under air. Isolated yields. [b] 5 mmol scale.

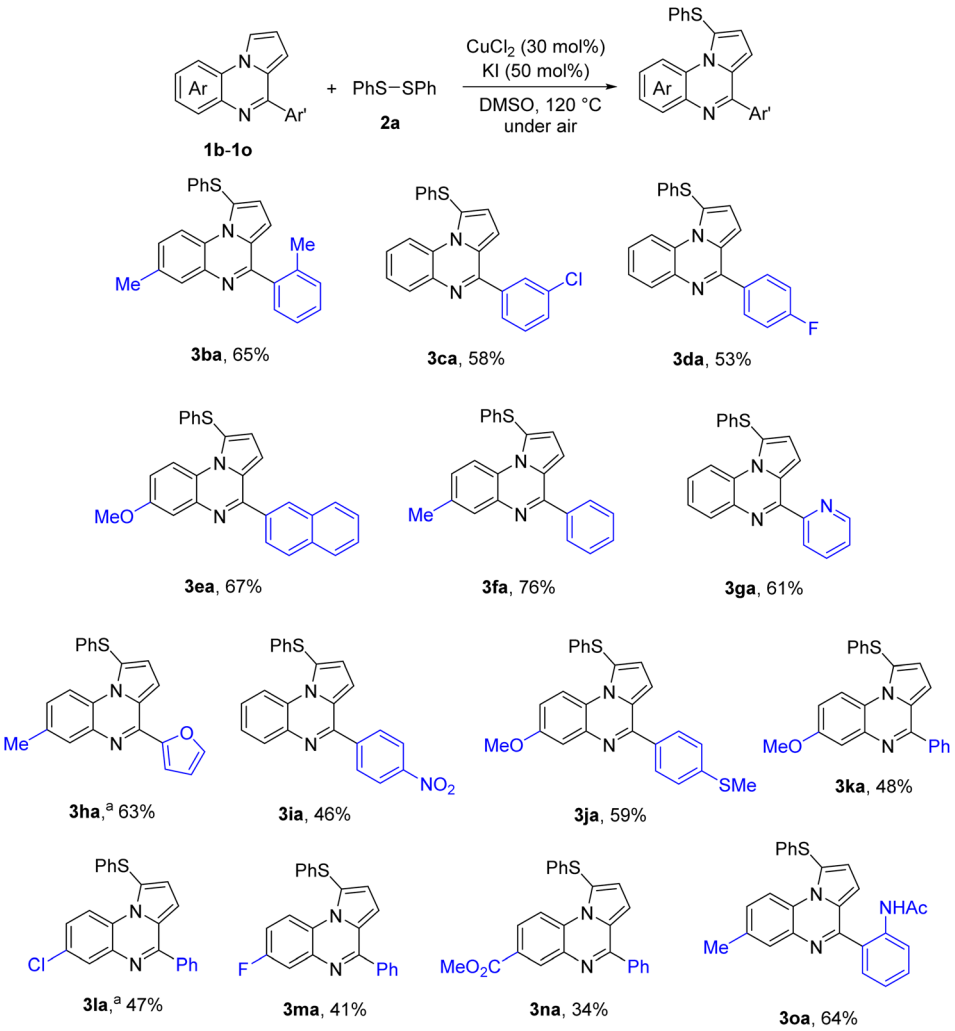
extremely low yield of **3aa** (entry 2), confirming the crucial role of the copper salt. Attempts to increase the yield of **3aa** by using other copper salts were unsuccessful (entries 3–5). Iron(III) chloride was inferior to $CuCl_2$ (entry 6). Some alternative iodides could be used, albeit affording **3aa** in relatively lower yields (entries 7 and 8). The reaction in the presence of I_2 gave **3aa** in 45% yield (entry 9). Without KI, only a small amount of **3aa** was obtained after column chromatography (entry 10). Sulfenylation of **1a** with **2a** under argon gave 60% yield of **3aa** (entry 11), implying the role of air as the co-oxidant. Lastly, replacing DMSO by other solvents gave low to moderate yields of **3aa** (entries 12–14).

Next scope of pyrrolo[1,2-*a*]quinoxalines was explored. The result is shown in Scheme 1. Overall, moderate to good yields of diaryl thioethers were obtained regardless of electronic properties of pyrrolo[1,2-*a*]quinoxalines. Functionalities such as fluoro (**3da**, **3ma**), chloro (**3ca**, **3la**), nitro (**3ia**), methylthio (**3ja**), ester (**3na**), and amide (**3oa**) groups were all compatible with reaction conditions. Heterocyclic substrates such as those containing pyridine (**3ga**) and furan (**3ha**) were also competent substrates.

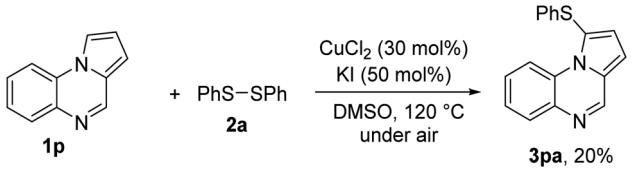
We questioned whether functionalization at C4 was crucial for successful sulfenylation. Thus, coupling of pyrrolo[1,2-*a*] quinoxaline **1p** with diphenyl disulfide **2a** was attempted (Scheme 2). As only 20% yield of the product **3pa** was obtained, substitution at C4–H bond with aromatics was important. At this stage, using C4-alkyl substituted pyrrolo[1,2-*a*]quinoxalines have not been examined.

Other diaryl disulfides rather than **2a** were also attempted. The result is shown in Scheme 3. Notably, use of di-heteroaryl disulfides such as **2c** did not affect the sulfenylation. A low yield of the sulfenylation product was obtained with respect to the acetoxylated disulfide (**3af**). Dialkyl disulfides were inactive toward the reaction conditions.

We next run some control experiments to have a better understanding of reaction mechanism (Scheme 4). In the absence of disulfide **2a**, no iodination of C1–H bond in **1a** was observed (eqn (1)). This result implied that the sequence of

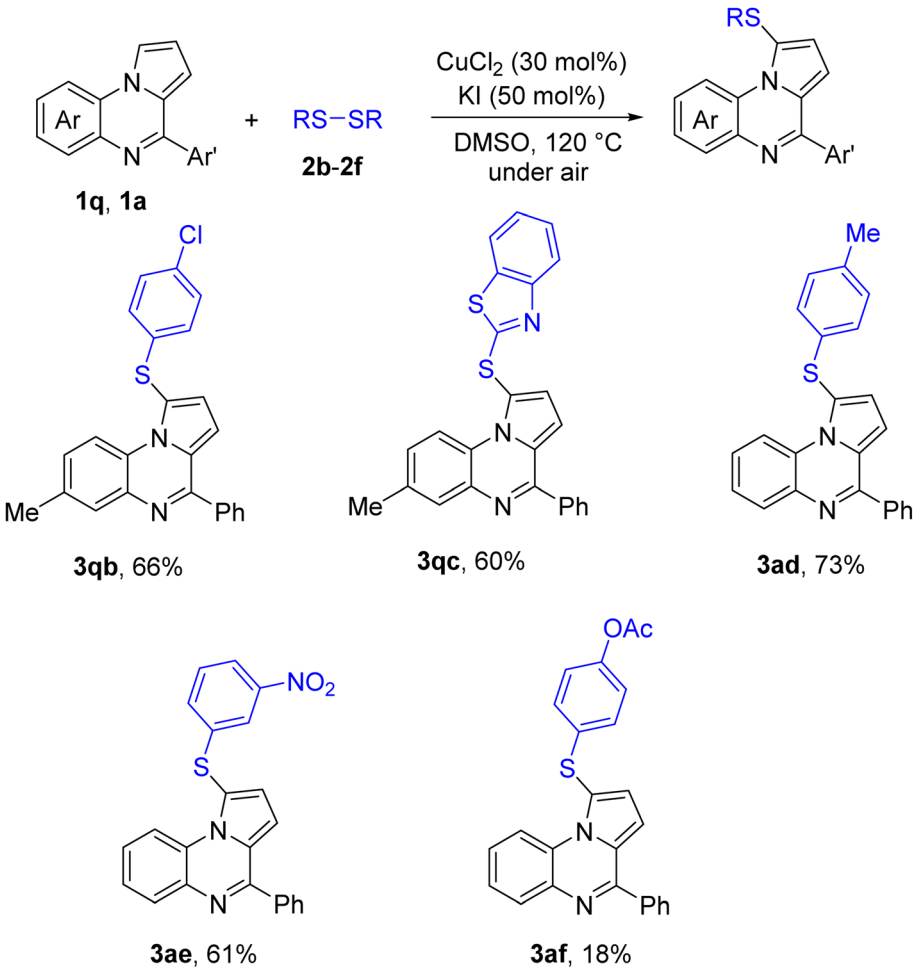


Scheme 1 Scope of pyrrolo[1,2-*a*]quinoxalines. *Reagents and conditions*: **1b–1o** (0.1 mmol), diphenyl disulfide **2a** (0.05 mmol), $CuCl_2$ (0.03 mmol), KI (0.05 mmol), DMSO (1 mL), 120 °C, 24 h, under air. Yields are isolated yields. [a]Diphenyl disulfide **2a** (0.075 mmol) was used.

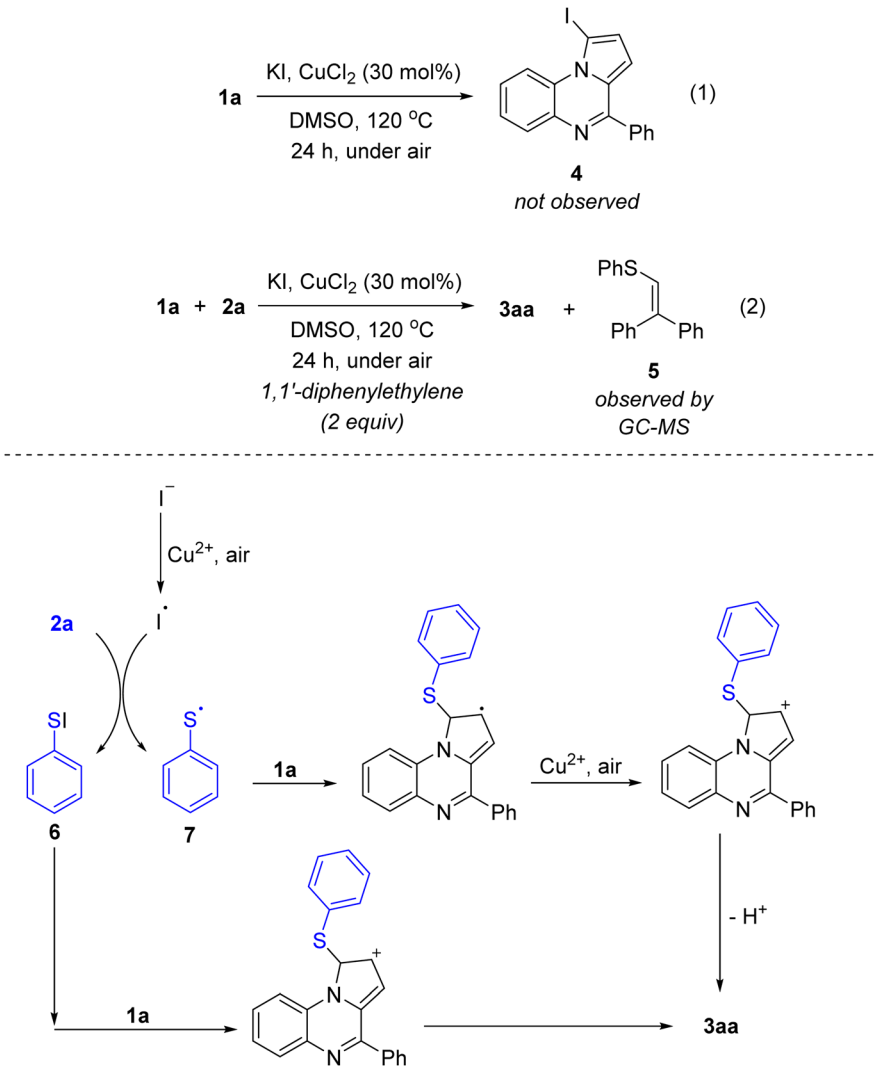


Scheme 2 Sulfenylation of pyrrolo[1,2-*a*]quinoxaline C1–H bond in the presence of C4–H bond.

electrophilic iodination followed by copper catalyzed activation of carbon–iodine bond was unlikely involved the reaction mechanism. Next, the addition of the radical quencher 1,1′-diphenylethylene (2 equivalents) did not completely suppress the sulfenylation (eqn (2)). Yet the small amount of vinyl sulfide **5** could be detected by GC-MS. Replacing diphenyl disulfide **2a** with thiophenol to couple with **1a** did not give the product **3aa**, revealing that thiophenol should not be the key sulfide source. Based on these results, a possible mechanism was proposed as that shown in Scheme 4. The iodide salt was oxidized in the presence of $CuCl_2$ and air to afford iodide radical, followed by the reaction with diphenyl disulfide **2a** to yield the adduct **6** and phenylthio radical **7**. Electrophilic substitution of **1a** with **6** followed by re-aromatization would afford the sulfenylation product **3aa**. Alternatively, radical addition of **7** to **1a** followed by oxidation and re-aromatization would also yield **3aa**. We envisaged that in the absence of air, DMSO could play a significant role in the oxidation steps.



Scheme 3 Sulfenylation of pyrrolo[1,2-*a*]quinoxaline C–H bonds with di(hetero)aryl disulfides. *Reagents and conditions*: pyrrolo[1,2-*a*]quinoxalines **1q**/**1a** (0.1 mmol), disulfides (0.075 mmol for **2b–2c**, 0.05 mmol for **2d–2f**), $CuCl_2$ (0.03 mmol), KI (0.05 mmol), DMSO (1 mL), 120 °C, 24 h, under air. Yields are isolated yields.



Scheme 4 Mechanistic consideration. *Reagents and conditions*: (eqn (1)) **1a** (0.1 mmol), $CuCl_2$ (0.03 mmol), KI (0.05 mmol), DMSO (1 mL), 120 °C, 24 h, under air; (eqn (2)) **1a** (0.1 mmol), **2a** (0.05 mmol), $CuCl_2$ (0.03 mmol), KI (0.05 mmol), 1,1′-diphenylethylene (0.2 mmol), DMSO (1 mL), 120 °C, 24 h, under air.

Conclusions

In conclusion, we have developed a method for direct sulfenylation of C1–H bonds in pyrrolo[1,2-*a*]quinoxalines with diaryl disulfides. The reactions featured mild conditions and excellent compatibility with a wide range of functionalities. Early thoughts on mechanism revealed a direct electrophilic sulfenylation which may include the formation of phenylthio radical intermediates.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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7 Please see the ESI for more details.†