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Transition metal-free direct C–H bond thiolation of 1,3,4-oxadiazoles and related heteroarenes†

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A convenient transition metal-free procedure for the direct thiolation of 1,3,4-oxadiazole C–H bonds using diaryl disulfides has been developed. Other substrates including indole, benzothiazole, *N*-phenylbenzimidazole, and caffeine were also thiolated in this manner, providing the corresponding products in good to excellent yields.

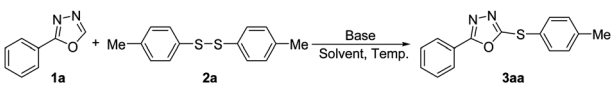
The formation of C–S bonds represents a key step in the synthesis of a broad range of biologically active molecules and functional materials.[1] In the past decade, the cross-coupling of aryl halides with thiols has become one of the dominant methods for the construction of C–S bonds. Complexes and salts of palladium,[2] nickel,[3] copper,[4] cobalt,[5] iron,[6] and indium[7] have been identified as efficient catalysts for these types of reactions. As an alternative to aryl halides, aryl triflates[8] and boronic acids[9] can be used as reaction partners in such transformations. The formation of C–S bonds has also been realised by coupling aryl halides with diaryl disulfides.[10] Although these traditional coupling reactions are effective in constructing various C–S bonds either metal–ligand combinations and/or prefunctionalised reaction partners are required, which significantly restricts potential applications of these methods.

Recently, major advances have been achieved in C–H bond functionalisation of 1,3,4-oxadiazoles.[11] These are relevant heterocycles because of their interesting properties in medicinal chemistry[12] and material sciences.[13] The 1,3,4-oxadiazole core is an important pharmacophoric substructure, and various derivatives show substantial bioactivities.[14] Although a few methods for the synthesis of heterocyclic thioethers containing 1,3,4-oxadiazole units and derivatives thereof are known,[4j,15] most of them require pre-functionalised 1,3,4-oxadiazoles and/or metal catalysts. Hence, the development of a transition metal-free protocol for C–S bond formations of non-activated 1,3,4-oxadiazoles appears desirable and synthetically attractive.[16] Here, we report progress along those lines and describe a method for direct thiolation of 1,3,4-oxadiazole C–H bonds using diaryl disulfides. Analogously, other heteroarenes including indole, benzothiazole, *N*-phenylbenzimidazole, and caffeine were converted to the corresponding thioethers.

The initial screening and optimization of the reaction conditions was conducted with 2-phenyl-1,3,4-oxadiazole (**1a**) and di-*p*-tolyl disulfide (**2a**) as substrates (Table 1). Assuming that a metal catalyst was needed, the first reaction was performed in the presence of CuI (20 mol%). Using **1a** and **2a** in a 1 : 2.5 ratio (on a 0.5 mmol scale), Cs_2CO_3 (2 equiv.) as base and toluene as solvent, product **3aa** was obtained in 47% yield after 18 h at 130 °C under argon (Table 1, entry 1). To our surprise, however, an increase in yield (54%) was observed in the absence of the copper salt (entry 2). With 5 equivalents of disulfide **2a** the yield of **3aa** was 77% (entry 3), and with 7 equivalents of **2a** this value remained the same (entry 4). Noteworthily, the excess of di-*p*-tolyl disulfide (**2a**) could be recovered quantitatively upon work-up.

Next, various solvents were screened for their influence on the reaction behaviour (entries 5–8). The reaction in acetonitrile gave a lower yield of **3aa**. No product was observed when DMSO and DMF were used. 1,4-Dioxane proved to be the best solvent, providing **3aa** in 87% yield (entry 8). Further studies

Table 1 Thiolation of 2-phenyl-1,3,4-oxadiazole (**1a**) with di-*p*-tolyl disulfide (**2a**)[a]



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

Entry	Base	Solvent	Temp. (°C)	Yield (%)
1[b]	Cs_2CO_3	Toluene	130	47
2	Cs_2CO_3	Toluene	130	54
3[c]	Cs_2CO_3	Toluene	130	77
4[d]	Cs_2CO_3	Toluene	130	77
5	Cs_2CO_3	CH_3CN	130	30
6	Cs_2CO_3	DMSO	130	0
7	Cs_2CO_3	DMF	130	0
8	Cs_2CO_3	1,4-Dioxane	130	87
9	NEt_3	1,4-Dioxane	130	0
10	*t*-BuOLi	1,4-Dioxane	130	0
11[e,f]	Cs_2CO_3	1,4-Dioxane	130	85
12[e]	Cs_2CO_3	1,4-Dioxane	110	83
13[g]	Cs_2CO_3	1,4-Dioxane	130	58
14[h]	Cs_2CO_3	1,4-Dioxane	130	86

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), base (1 mmol), solvent (2 mL), 130 °C, argon atmosphere, 18 h. [b] Addition of 20 mol% of CuI. [c] Use of 5 equiv. of **2a**. [d] Use of 7 equiv. of **2a**. [e] 24 h. [f] Use of 1.3 equiv. of Cs_2CO_3. [g] Performed in air. [h] The purity of Cs_2CO_3 was 99.994%.

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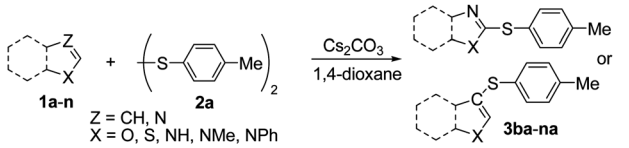
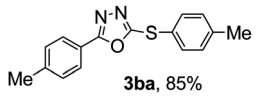
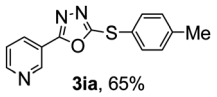
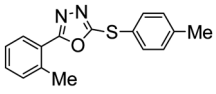
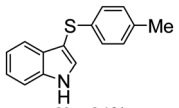
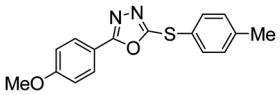
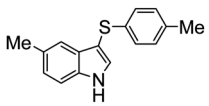
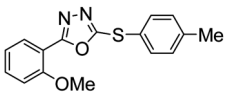
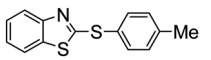
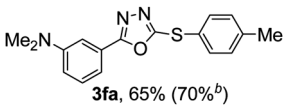
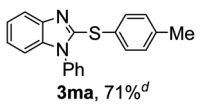
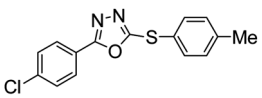
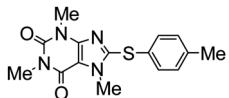
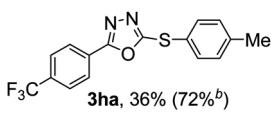
† Electronic supplementary information (ESI) available: Experimental details and spectroscopic data as well as NMR spectra. See DOI: 10.1039/c2cc36711d

Table 2 Thiolation of 1,3,4-oxadiazoles and related heteroarenes with di-*p*-tolyl disulfide (**2a**)[a]



Entry	Product, yield	Entry	Product, yield
1	 **3ba**, 85%	8	 **3ia**, 65%
2	 **3ca**, 80%	9	 **3ja**, 91%
3	 **3da**, 60% (73%[b])	10	 **3ka**, 93%
4	 **3ea**, 71%	11	 **3la**, 55%[c] (86%[d])
5	 **3fa**, 65% (70%[b])	12	 **3ma**, 71%[d]
6	 **3ga**, 75% (65%[b])	13	 **3na**, 55%[d]
7	 **3ha**, 36% (72%[b])		

[a] Reaction conditions: heteroarene (0.5 mmol), **2a** (1.25 mmol), Cs_2CO_3 (1 mmol), 1,4-dioxane (2 mL), 130 °C, argon atmosphere, 18 h. [b] Performed at 110 °C for 24 h. [c] Reaction time of 10 days. [d] Use of 3 equiv. of *t*-BuOLi as base instead of Cs_2CO_3; reaction time of 32 h.

showed that the use of other bases such as triethylamine and *t*-BuOLi was ineffective (entries 9 and 10). Using less base or performing the reaction at lower temperature decreased the yield of **3aa** slightly, and after 24 h, the product was obtained in 85% and 83% yields, respectively (entries 11 and 12). In air instead of argon, the yield of **3aa** dropped to 58% (entry 13). To exclude a possible catalytic effect of a trace metal contamination,[17] a control experiment was performed using Cs_2CO_3 with a purity of 99.994% and freshly distilled 1,4-dioxane. The yield of 86% (entry 14) made it unlikely that a trace metal was involved in these reactions.

In Table 2 the screening results with respect to the substrate scope are shown. Various 2-aryl substituted 1,3,4-oxadiazoles and related heterocycles were reacted with disulfide **2a** under the previously optimized reaction conditions. In general, good to high yields of the corresponding thiolated products were obtained. A straightforward correlation between the stereoelectronic properties of the substrate and the reaction efficiency could not be deduced. It appeared, however, as if 2-aryl-1,3,4-oxadiazoles with electron-donating substituents on the arene gave higher yields than those with electron-withdrawing groups. For example, while tolyl-substituted products **3ba** and **3ca** were obtained in 85% and 80% yield, respectively, trifluoromethyl derivative **3ha** was isolated in only 36% yield (Table 2, entries 1 and 2 *versus* entry 7). In the latter case, the yield could be improved to 72% by performing the reaction at a slightly lower temperature (110 °C) for an extended reaction time (24 h). While this modification of the reaction conditions was beneficial for the preparation of product **3da** (entry 3; 60% *versus* 73%) too, it proved to be disadvantageous in the synthesis of **3ga**. There, the original conditions were better (entry 6: 75% *versus* 65%). The 1,3,4-oxadiazole series was completed by the preparation of 2-(3-pyridyl)-substituted product **3ia**, which was obtained in 65% yield indicating that such a heteroaryl group in the 2 position of the substrate was tolerated well (entry 8).

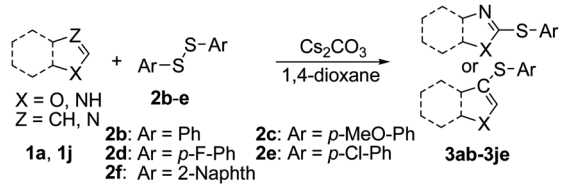
To extend the substrate scope, related heterocycles were applied and reacted with di-*p*-tolyl disulfide (**2a**) to produce the corresponding heteroaryl thioethers (Table 2, entries 9–13). To our delight, indole and its 5-methylated derivative gave 3-thiolated products **3ja** and **3ka** in very high yields (91% and 93%, respectively; entries 9 and 10). Those results compare well to the known metal-catalysed procedure for the synthesis of 3-sulfenyl indoles.[18] The reaction of benzothiazole with **2a** was slow, affording **3la** in only 55% yield after 10 days. Changing the base from Cs_2CO_3 to *t*-BuOLi, however, shortened the reaction time to 32 h and increased the yield to 86% (entry 11). Similarly, with *t*-BuOLi as base, *N*-phenylbenzimidazole and caffeine were directly thiolated to afford the corresponding products **3ma** and **3na** in 71% and 55% yields, respectively (entries 12 and 13).

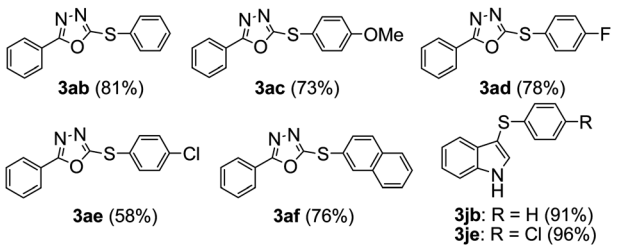
Next, the diaryl disulfide component was varied and 2-phenyl-1,3,4-oxadiazole (**1a**) and indole (**1j**) served as coupling partners (Table 3). Accordingly, thiolation of **1a** with diphenyl-, 4,4′-dimethoxydiphenyl-, 4,4′-difluorodiphenyl-, 4,4′-dichlorodiphenyl- and 2,2′-dinaphthyl-substituted disulfides (**2b–2f**) provided **3ab–3af** in yields ranging from 58% to 81%. Indole (**1j**) reacted with diaryl disulfides **2b** and **2e** to give the corresponding products (**3jb** and **3je**) in 91% and 96% yield, respectively.[19] Subsequent screenings showed that dibenzyl disulfide and bis(4-nitrophenyl) disulfide did not react with **1a** under the given reaction conditions.

With respect to the reaction mechanism we assume that a deprotonation of the heterocycle occurs providing an anion, which reacts with the diaryl disulfide by nucleophilic attack, resulting in C–S bond formation.[20,21]

In conclusion, we developed a facile procedure for the synthesis of heterocyclic thioethers under transition metal-free conditions. Various 2-aryl-1,3,4-oxadiazoles were thiolated at C5 in good to high yields using diaryl disulfides as the aryl sulfide source. Also aryl thiols could be applied, albeit the product yields were only moderate.[19] Finally, the method proved applicable to other heterocycles providing thioethers from indole, benzothiazole, *N*-phenylbenzimidazole, and caffeine in good yields.

Table 3 Scope of diaryl disulfide coupling partners[a]





[a] For the reaction conditions, see Table 1, entry 8.

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19 The thiolation can also be performed with aryl thiols instead of diaryl disulfides. For details, see the ESI†.

20 With indole (**1j**) as the starting material, the reaction should be initiated by NH deprotonation.

21 For an analogous substitution reaction starting from indane-1,3-diones, see: D. Giles, M. S. Prakash and K. V. Ramseshu, *Eur. J. Chem.*, 2007, **4**, 428.