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SHORT COMMUNICATION

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Near Room Temperature Cross-Coupling Reactions of Arene Boronic Acids with a Quinoxaline 1,4-Dioxide Benzylsulfanyl Derivative

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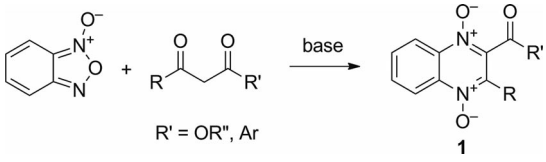
A new quinoxaline 1,4-dioxide benzylsulfanyl derivative was tested under mild conditions in copper-mediated Liebeskind–Srogl (LS) cross-coupling reactions with arene boronic acids. These first organometallic cross-coupling reactions performed on a quinoxaline 1,4-dioxide derivative open new perspectives in medicinal chemistry. They represent also the first LS cross-couplings run with an electrophile equipped with an aryl *N*-oxide moiety.

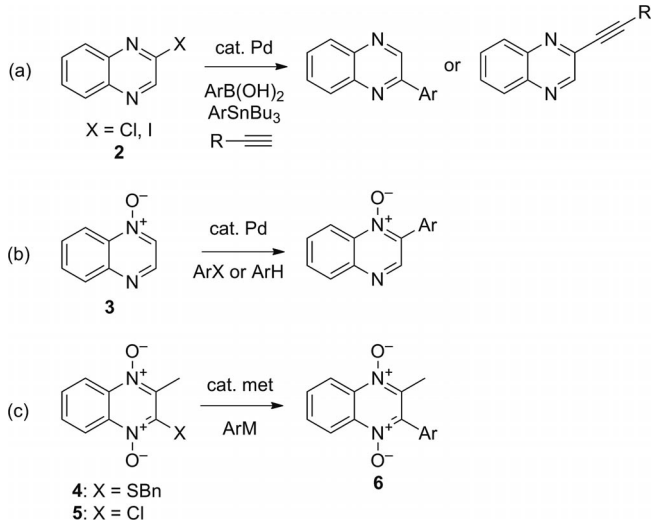
Introduction

Heteroaryls derived from the quinoxaline 1,4-di-*N*-oxide scaffold such as compounds **1** are well represented in medicinal chemistry. These compounds are endowed with many biological properties that mainly encompass the properties of their mono- or non-oxygenated homologs.[1,2] Apart from their antibacterial and antiprotozoal properties, members of this group have recently been in the limelight because of their potential as prodrugs against hypoxic cancerous cells associated with increased resistance to radiation and chemotherapy.[3] For many years, the synthesis of quinoxaline dioxides has mainly relied on the condensation of benzofuroxan derivatives with 1,3-diketones or β-keto-esters under basic conditions (Scheme 1), as originally described by Issidorides and Haddadin from Beirut University.[4] The so-called Beirut reaction was extended further to the synthesis of 2-sulfanyl-[5] and 2-dialkylphosphonyl-[6] quinoxaline 1,4-dioxide derivatives.



Scheme 1. Formation of quinoxaline 1,4-dioxides by the Beirut reaction.

In medicinal chemistry, the preparation of a wide range of quinoxaline 1,4-dioxide analogs by making use of this reaction can rapidly become tedious, as it implies the repetition of condensation reactions from the starting material. A more elegant approach, which has not been explored yet, would rely on the transition-metal-catalyzed derivatization of an electrophilic quinoxaline 1,4-dioxide precursor. To the best of our knowledge, only either non-oxygenated 2-haloquinoxaline derivatives like **2** or quinoxaline monoxide **3** have been involved so far in transition-metal-catalyzed cross-coupling reactions: compound **2** has been engaged in a few Suzuki, Stille, and Sonogashira reactions (Scheme 2a),[7] whereas **3** has recently been subjected to palladium-catalyzed cross-coupling reactions involving direct C–H activation of its most acidic C–H bond (Scheme 2b).[8] Although quite elegant, this latter method initiated by Fagnou et al. is not recommended for the preparation of thermally sensitive molecules, as it requires temperatures over 100 °C.



Scheme 2. Organometallic cross-coupling reactions involving quinoxaline derivatives: (A) see ref.[7]; (b) see ref.[8]; (c) our work.

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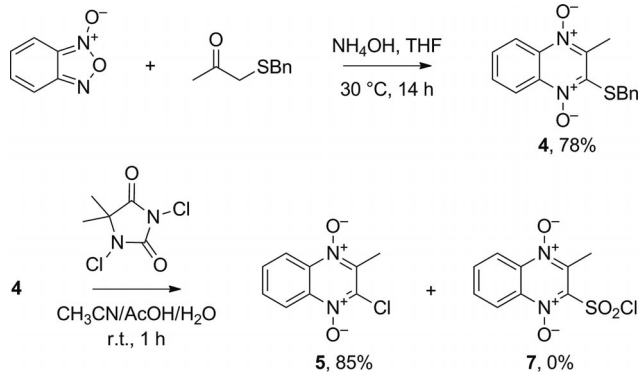
We present here our organometallic cross-coupling reactions aimed at preparing 2-arylated quinoxaline 1,4-dioxide derivatives of type **6** mainly from novel benzylsulfanyl derivative **4** (Scheme 2c). This sulfurylated derivative was engaged in palladium-catalyzed cross-coupling reactions with arene boronic acids in the presence of an excess amount of copper(I) thiophene-2-carboxylate (CuTC), that is, by using conditions initially developed by Liebeskind and Srogl for the cross-couplings of (hetero)aromatic thioethers.[9] Although no sulfurylated heteroaryl *N*-oxides have been investigated so far in Liebeskind–Srogl (LS) reactions, nonaromatic thioimidate *N*-oxides have been shown to react with phenylboronic acid in the presence of 2 equiv. of copper(I) 3-methylsalicylate (CuMeSal).[10] For comparison, we also describe here the organometallic cross-couplings of already known 2-chloride **5**.[5a,5b]

Results and Discussion

We first prepared benzylsulfanyl derivative **4** by using the Beirut reaction, as already advocated for the synthesis of quinoxaline thioether derivatives.[5] Although ammonia gas was previously recommended for this transformation,[5] we obtained a very good yield of **4** by simply making use of concentrated aqueous ammonia in THF (Scheme 3). With other bases like cesium carbonate or calcium hydroxide in THF, only very poor yields of **4** were obtained. At this stage, direct and high-yielding access to 2-chloride **5** was easily obtained simply by treating **4** with 2 equiv. of 2,4-dichloro-5,5-dimethylhydantoin under conditions originally reported for the mild conversion of benzylic sulfides into the corresponding chlorosulfonyl derivatives.[11] In our case, chlorosulfonyl quinoxaline 1,4-dioxide **7** could not be detected by analyzing the reaction crude mixture by NMR spectroscopy.[12] This new procedure for the preparation of **5** appears much milder than the previously reported two-step protocol, which relies on the oxidation of the quinoxaline thioether derivative into the corresponding sulfone prior to treatment with hot concentrated HCl.[5a,5b]

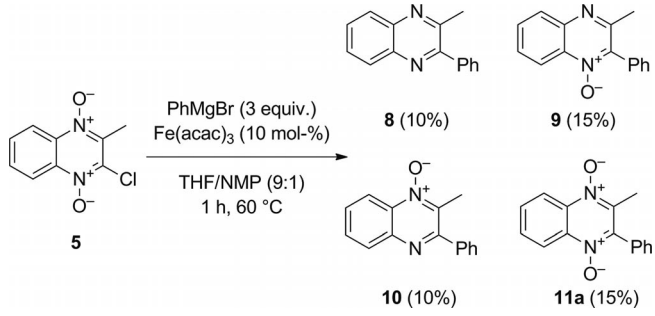


Scheme 3. Preparation of electrophilic quinoxaline 1,4-dioxides **4** and **5**.

We began our study by investigating Suzuki–Miyaura cross-coupling reactions between tolylboronic acid and 2-chloro-3-methylquinoxaline 1,4-dioxide (**5**) by using sodium carbonate as a base and $Pd(PPh_3)_4$ as a catalyst, as advocated for the cross-couplings of 2,3-dichloroquinoxaline[7f] or 2-chloropyridine *N*-oxide derivatives.[13] Despite our efforts, by varying the solvent (THF or DMF), the temperature, and the reaction time we could not detect any trace amounts of the desired 2-tolyl-quinoxaline 1,4-dioxide. As similar negative results were obtained when we used $Pd(OAc)_2$ in the presence of PPh_3 or dppf in place of $Pd(PPh_3)_4$, we did not explore this kind of cross-coupling any further.

We rather turned our attention to the iron-catalyzed cross-coupling reactions of **5** with phenylmagnesium bromide by using either THF alone or a mixture of THF and *N*-methylpyrrolidone (NMP) as the solvent and $[Fe(acac)_3]$ as the catalyst, as recommended for the arylation of heteroaryl chlorides (including 2-chloroquinoxaline) by Grignard reagents.[14]

Although we ran many experiments, varying the temperature (from –10 to 60 °C), the number of equivalents of phenylmagnesium bromide (2–4 equiv.), as well as the time of the reaction (1 h–18 h), the results were also quite disappointing, as in most cases only complex mixtures were obtained. In the most favorable experiment run at 60 °C over 1 h, we could isolate expected dioxide **11a** in low yield (15%) next to 2-methyl-3-phenylquinoxaline (**8**) and monoxides **9** and **10** (Scheme 4).[15] This tendency to yield deoxygenated derivatives was also observed in trials run at lower temperatures.

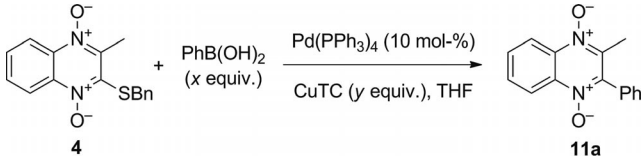


Scheme 4. Iron-catalyzed cross-coupling reaction.

At this stage, rather than investigating cross-coupling reactions starting from other 2-haloquinoxaline 1,4-dioxides in place of **5**,[16] we decided to study the reactivity of benzylsulfanyl derivative **4** in LS cross-coupling reactions with boronic acids, in the hope that the mild and neutral conditions used would prevent the formation of deoxygenated compounds. Optimization of the reaction conditions was performed with phenylboronic acid (Table 1).

Our preliminary experiment (Table 1, Entry 1) conducted at 50 °C with about 1 equiv. of both the boronic acid and CuTC was encouraging, as it gave the expected cross-coupling compound in the same yield as the best experiment run with chloride **5**. We were in particular pleased to find

Table 1. Optimization of the LS cross-coupling reaction.



4 11a

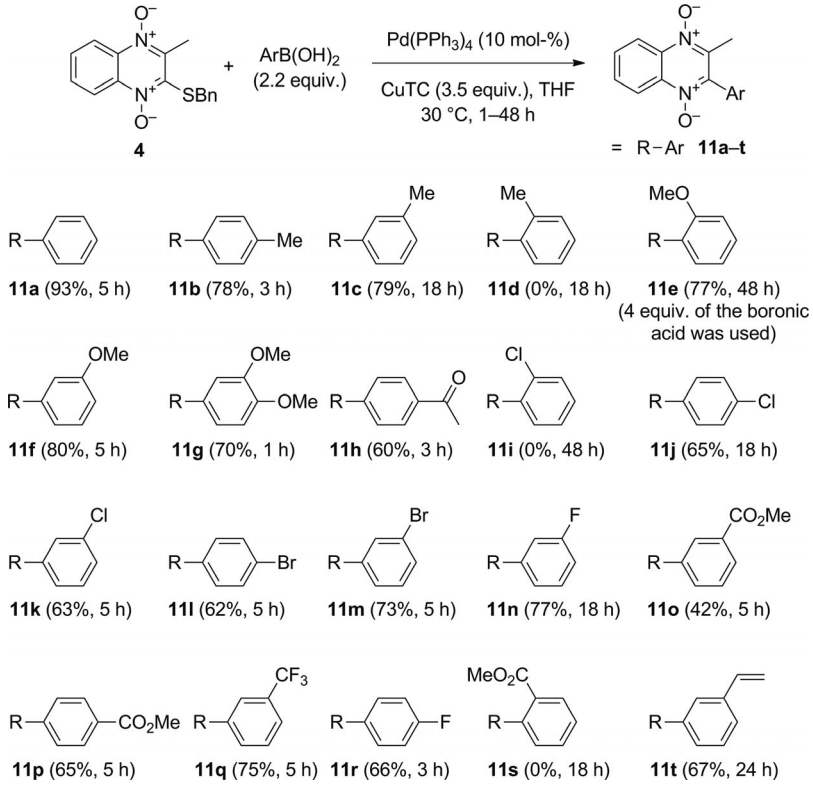
Entry	*x*/*y*	*t* [h]	*T* [°C]	**4**/**11a**[a]	Yield [%][b]
1	1.1:1.3	18	50	68:32	15
2	2.2:2.2	18	30	66:34	20
3	2.2:3.5	18	30	0:100	89
4	1.1:3.5	18	30	5:95	72
5[c]	2.2:3.5	18	30	5:95	26[d]
6	2.2:0.0	18	30	100:0	n.d.[e]
7	2.2:3.5	48	20	60:40	25
8[f]	2.2:3.5	48	20	95:5	3
9	2.2:3.5	5	30	5:95	93

[a] Estimated by NMR spectroscopy. [b] Isolated yield. [c] CuMeSal was used instead of CuTC. [d] Several unidentified quinoxaline derivatives were present. [e] Starting compound **4** was entirely recovered. [f] $PhBF_3^-K^+$ was used in place of $PhB(OH)_2$.

in the NMR spectrum of the crude mixture that essentially only starting material **4** was present and no trace amounts of deoxygenated derivatives **8**–**10** were observed. About the same result was obtained at 30 °C with nearly 2 equiv. of both CuTC and phenylboronic acid (Table 1, Entry 2). Raising the number of equivalents of CuTC to 3.5 was key to obtaining a very good yield of **11a** (Table 1, Entry 3), whereas starting benzylsulfanyl derivative **4** was entirely recovered in the absence of CuTC (Table 1, Entry 6). By employing 1.1 equiv. of the boronic acid in the presence of 3.5 equiv. of CuTC, a good yield of **11a** was also obtained, though not as high as that obtained with 2.2 equiv. of the boronic acid (Table 1, Entry 4). Switching from CuTC to CuMeSal (another copper reagent sometimes used in LS couplings) was detrimental, as we only could isolate **11a** in low yield (Table 1, Entry 5). At room temperature, with 2.2 equiv. of phenylboronic acid and 3.5 equiv. of CuTC, the reaction appeared much more sluggish, leading to **11a** in only modest yield after 2 d (Table 1, Entry 7), and by using potassium phenyltrifluoroborate in place of phenylboronic acid, the reaction practically did not occur (Table 1, Entry 8). Finally, when the reaction was run with 2.2 equiv. of phenylboronic acid and 3.5 equiv. of CuTC at 30 °C over only 5 h, starting quinoxaline dioxide **4** was almost completely consumed and the desired cross-coupling product was obtained in excellent yield (Table 1, Entry 9).

Applying these optimized conditions, we examined the scope of the LS cross-coupling reaction between **4** and arene boronic acids (Scheme 5).

As the results shown in Scheme 5 attest, this method is compatible with a variety of arene boronic acids possessing either electron-donating or electron-withdrawing groups in the *meta* or *para* position. Notably, the tolerance for chloride or bromide on the arene moiety in this LS reaction offers an opportunity for envisioning subsequent cross-coupling reactions.



Scheme 5. Synthesis of 2-methyl-3-aryl-quinoxaline 1,4-dioxides. Reactions were monitored by NMR spectroscopy. Yield of the isolated product is reported.

Arene boronic acids bearing a substituent in the *ortho* position did not effectively undergo the cross-coupling reaction with **4**. We were unable to isolate **11d**, **11i**, or **11s** after 18 h of reaction at 30 °C and a good yield of **11e** was realized only when forcing conditions were used. This sensitivity of LS couplings to steric hindrance has already been reported.[8c]

Conclusions

In summary, we have for the first time developed an organometallic cross-coupling reaction involving a quinoxaline 1,4-dioxide partner. For that purpose, new sulfurylated quinoxaline 1,4-dioxide electrophilic derivative **4** was readily prepared from commercially available compounds. Whereas chloride **5** did not give satisfactory results, either in Suzuki–Miyaura or in iron-catalyzed cross-coupling involving tolylboronic acid or phenylmagnesium bromide, respectively, much more convincing results were obtained with benzylsulfanyl derivative **4**. Indeed, this sulfurylated compound was found to react quite efficiently under neutral conditions and at near room temperature in LS-type cross-couplings with a variety of arene boronic acids, in the presence of a catalytic amount of $Pd(PPh_3)_4$ and at least 3 equiv. of CuTC. The necessity, in our case, of a large excess amount of a copper(I) salt contrasts with typical LS cross-couplings, which are usually operational with only 1 equiv. of CuTC and can probably be explained by the ability of the *N*-oxide groups to form a complex with a copper(I) salt.[17] Apart from offering an extension to the chemistry of quinoxaline 1,4-dioxides, our work widens the scope of LS cross-coupling reactions which, to the best of our knowledge, have not been performed yet with an electrophilic partner possessing an aryl *N*-oxide moiety. We will continue to explore the scope of our method by testing heteroarylboronic acids in place of arene boronic acids.

Supporting Information (see footnote on the first page of this article): Experimental procedures and copies of the ^1H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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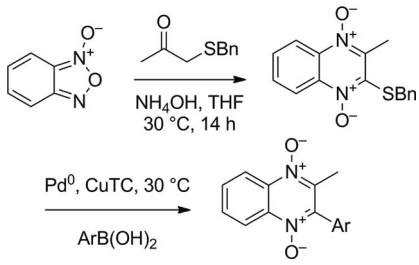
A mild an efficient protocol was developed to prepare quinoxaline 1,4-dioxide derivatives. A benzylsulfanyl quinoxaline 1,4-dioxide derivative was engaged as an electrophilic partner in copper-mediated Liebeskind–Srogl cross-coupling reactions with a wide range of arene boronic acids. These experiments represent the first organometallic coupling reactions on quinoxaline 1,4-dioxide derivatives



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