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Building Block Approach for the Synthesis of Sulfoximines

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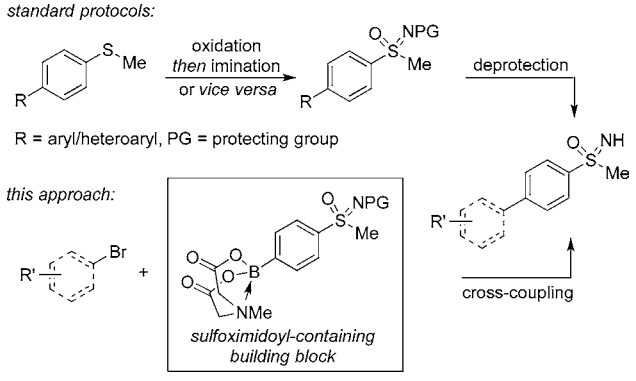
Supporting Information

ABSTRACT: A cross-coupling strategy for the preparation of novel sulfoximines via preformed sulfoximidoyl-containing building blocks has been developed. It allows obtaining a wide range of products in good yields under mild reaction conditions, and it can be applied in late-stage functionalizations, as demonstrated by the synthesis of a sulfoximine-based analogue of a recently reported potent valosine-containing protein inhibitor.

The growing interest of applying sulfoximines[1] in medicinal chemistry[2] and crop protection[3] has prompted the development of new strategies for the incorporation of sulfoximidoyl moieties in functionalized molecules. The majority of sulfoximine syntheses start from the corresponding sulfide, which is oxidized and imidated[4] in discretionary order. In most cases, the resulting sulfoximines are N-protected, and an additional step to reach the free *N*H-sulfoximine is required (Scheme 1, top). In addition to developing various protocols for the synthesis[5] and further functionalization[6] of sulfoximines, we have interest in the preparation of sulfoximidoyl-containing analogues of bioactive compounds.[7] In general, the latter molecules exhibit a high density of functional groups, and for the synthetic efficiency, it is critical in which phase of the synthesis the sulfoximidoyl moiety is introduced. For example, if installed late, the chemical complexity of the molecular backbone might hamper the aforementioned sulfur oxidation/imination sequence. If introduced early, a sulfoximidoyl group can either affect the subsequent synthetic steps or, in the worst case, be degraded. In the light of this situation, preformed bench-stable sulfoximidoyl-containing building blocks, which could be integrated into a target structure at a late stage of a synthesis could offer attractive solutions (Scheme 1, bottom).

Scheme 1. Previous and Newly Developed Preparation of *NH*-Sulfoximines



Biaryl or heteroaryl units are important scaffolds in bioactive compounds. In many cases, these motifs are introduced by Suzuki−Miyaura couplings, which have proven to be robust and industrially applicable.[8] The success of these carbon−carbon bond formations depends significantly on the type of boron reagent and the reaction conditions, which have to be carefully fine-tuned.[9] With the vision of developing a building block approach toward diaryl-containing sulfoximines,[10] we felt attracted to the work of Burke,[11] who has established the use of *N*-methyliminodiacetic acid (MIDA) boronates in such cross-coupling reactions. Being stable to air, moisture, and silica gel, these N-coordinated cyclic boronic esters appeared most promising for our strategy. The first results of this study, which involved the syntheses of novel MIDA boronates bearing sulfoximidoyl substituents, are illustrated here.[12]

The work by Burke[11f,g] suggested two routes toward thioanisyl MIDA boronates **2**, which we considered as key intermediates for the syntheses of target structures **6** (Scheme 2). They differed in the starting material. While route A made use of thioanisyl bromoarenes **1**, route B started from the corresponding boronic acids **4**. Both led to target compounds **6**, but the overall efficiency of route B was higher (considering the product yields and the process practicability). For example, treatment of *para*-substituted methyl sulfide **1a** with triisopropylborate and *n*BuLi in THF at −78 °C followed by transligation with MIDA (**3**) in hot DMSO gave *para*-thioanisyl MIDA boronate **2a** in 30% yield (route A), whereas applying boronic acid **4a** in the reaction with **3** (route B) led to **2a** in 88% yield. Analogously, starting from *meta*-substituted **1b**, *meta*-thioanisyl MIDA boronate **2b** was obtained in 68% yield (route A), while the same product was isolated in 73% yield when boronic acid **4b** was applied following route B. The *ortho*-substituted **4c** gave *ortho*-thioanisyl MIDA boronate **2c** in 81% yield. All three thioanisyl MIDA boronates **2a−c** could smoothly be oxidized to the

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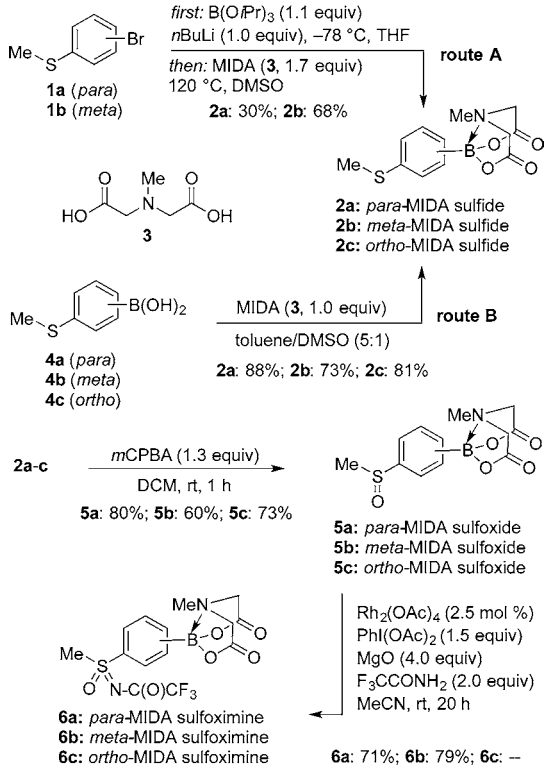
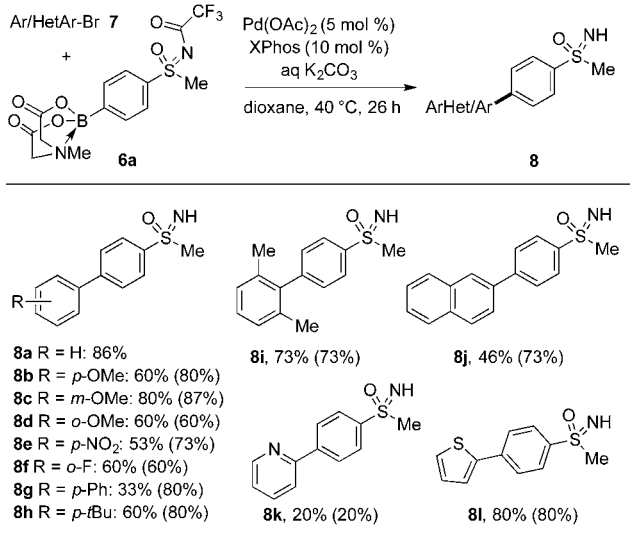
Scheme 2. Syntheses of Sulfoximidoylic Building Blocks 6a and 6b



corresponding sulfoxides **5a–c** using *m*CPBA in DCM at ambient temperature (Scheme 2). For the final step, a rhodium-catalyzed imination procedure developed in our group[13] was selected. The mild reaction conditions allow sulfoxide iminations with readily available reagents and low catalyst loading (2.5 mol %) at room temperature, leading to *N*-trifluoroacetyl-protected sulfoximines, which are synthetically privileged due to their relative stability and ease of deprotection. While the imination of **2a** and **2b** proceeded well, leading to *para*- and *meta*-sulfoximidoyl MIDA boronates **6a** and **6b** in 71 and 79% yield, respectively, only traces of *ortho*-substituted **6c** were observed (by NMR spectroscopy) in the attempt to convert thioanisyl MIDA boronate **2c**.[14] Presumably, the steric hindrance induced by the bulky MIDA boronyl group *ortho* to the sulfoxide moiety hampered the imination process.

With building blocks **6a** and **6b** in hand, Suzuki–Miyaura coupling processes with aryl bromides were investigated to validate the overall concept for the preparation of diaryl-containing *NH*-sulfoximines. After several reaction parameters were screened (temperature, catalyst, and base; for details, see Supporting Information) with bromobenzene and *para*-sulfoximidoyl MIDA boronate **6a** as representative starting materials, the optimal reaction conditions involved the use of $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %), and K_2CO_3 (aqueous solution) in dioxane under an argon atmosphere at 40 °C for 26 h. Under these conditions, coupling product **8a** was obtained in 86% yield (Scheme 3).[15,16] Other aryl/heteroaryl bromides reacted well with MIDA boronate **6a**, too, and in general, the target products were isolated in good yields. Electronic factors appeared to have only a minor effect on the coupling. Comparing the yields of **8b–d** indicated a negative influence of an *ortho*-substituent. Nevertheless, using 2,6-dimethylbromobenzene led to sulfoximine **8i** in 73% yield. Also, heteroaryl bromides could be applied,

Scheme 3. Coupling between MIDA Boronate 6a and Various Aryl and Heteroaryl Bromides

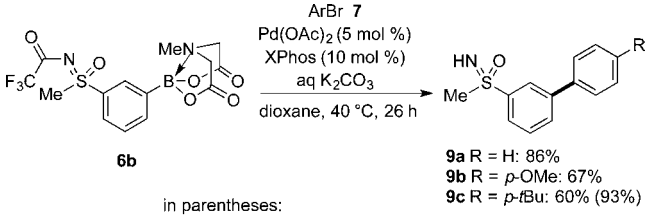


in parentheses: yields after treatment with K_2CO_3 in MeOH (for details see text)

but the structural features played an important role, as revealed by the very different results in the formation of 2-pyridinyl- and 2-thiophenyl-substituted products **8k** and **8l**, which were obtained in 20 and 80%, respectively. In several cases, the crude product mixture contained significant amounts of the corresponding *N*-trifluoroacetyl-substituted sulfoximine, revealing an incomplete cleavage of the protecting group during the reaction and the subsequent workup. In those cases, the yield of the desired *NH*-sulfoximine could be increased by stirring the crude reaction mixture in methanol in the presence of K_2CO_3 for 2 h at room temperature. Most significantly, by following this protocol, modification of the yield of **8g** increased from 33 to 80% (Scheme 3).

Retaining the reaction conditions, couplings with *meta*-sulfoximidoyl MIDA boronate **6b** were studied next (Scheme 4). This building block was also suitable, and products **9a–c** were obtained in yields between 67 and 93%.[17]

Scheme 4. Couplings Involving MIDA Boronate 6b



in parentheses:
yield after treatment with K_2CO_3 in MeOH (for details see text)

Finally, we intended to demonstrate the synthetic value of the newly devised building block approach by a late-stage functionalization of a more complex molecule containing multiple heteroatoms. Along these lines, we felt attracted by sulfone **10**, which was shown to be a potent and selective valosine-containing protein (VCP) inhibitor with significant antiproliferative activity (Scheme 5).[18] Structurally, **10** is characterized by its 1,2,4-triazole core, the 3-pyridinyl substituent at the 3 position of the heterocycle, and the ether and thioether linkages. Considering the potential of a bioisosteric replacement of the sulfonyl group by a sulfoximidoyl moiety,[2] we envisaged

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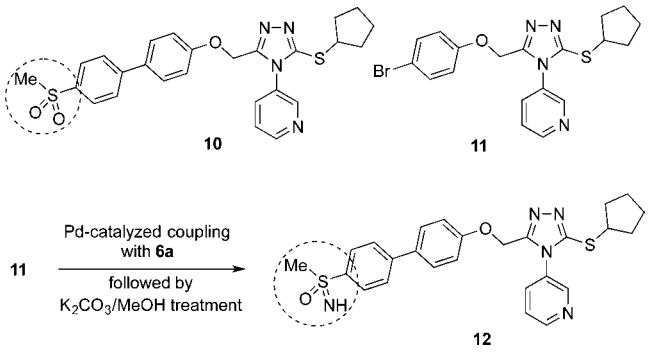
Scheme 5. Synthesis of *NH*-Sulfoximine 12: Analogue of the VCP Inhibitor 10



the synthesis of sulfoximine **12** following the previously introduced building block strategy. To our delight, the approach proved successful, providing **12** by coupling of **6a** with aryl bromide **11**. Although the yield of **12** was low (15%), we considered the preparation of this compound a success as it provided sufficient product quantities for potential biological tests.

In summary, we developed sulfoximidoylic building blocks, which can be used for synthesizing diaryl-containing *NH*-sulfoximines by Suzuki−Miyaura-type cross-couplings and late-stage functionalizations. Applying these air- and moisture-stable molecular scaffolds in automated synthesis will rapidly expand the sulfoximine portfolio and advance library synthesis.[19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02678.

Experimental procedures, analytical data, and NMR spectra of the presented products (PDF)

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Notes

The authors declare no competing financial interest.

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(15) The attempt to apply a sulfoximidoyl-substituted pinacol boronic acid ester analogous to **6a** gave an unsatisfying result.
(16) During the coupling process, partial protodeboronation occurred, and the presence of the byproducts impeded the cleaning process by column chromatography. Performing the coupling reactions at 40 °C minimized this side reaction.
(17) As *meta*-sulfoximidoyl MIDA boronate **6c** remained inaccessible, we investigated the cross-coupling of the corresponding sulfoxide **5c** with bromobenzene. The reaction proceeded well, providing 2-biphenyl methyl sulfoxide in 87% yield. Attempts to iminate this product by the aforementioned rhodium catalysis led to only trace quantities of the expected sulfoximine (as proven by ^{1}H NMR spectroscopy and mass spectrometry).
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