Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Tetrahydrobenzo[c]thieno[2,1-e]isothiazole 4-Oxides: Three-Dimensional Heterocycles as Cross-Coupling Building Blocks

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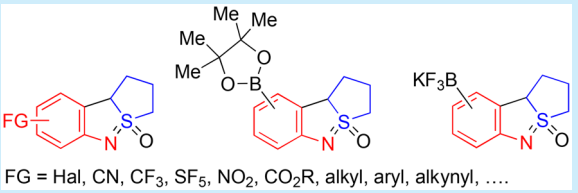
Supporting Information

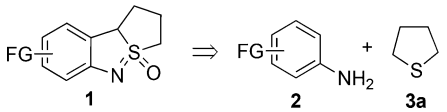
ABSTRACT: Unprecedented three-dimensional heterocycles are introduced, and their scaffold functionalization is described. A robust synthetic method utilizing cheap commercially available starting materials leads to a wide range of products on gram scale. The product portfolio can be expanded by applying newly devised building blocks with relevance for automated parallel synthesis in cross-coupling reactions.



In 2009, Pitt and co-workers generated a "virtual exploratory heterocyclic library" (VEHICLe) containing 24847 mono- and bicyclic ring systems.[1] To their surprise, only 1701 of them had ever been synthesized, and very few of them were routinely used in approaches toward drug-like molecules. This very low level of diversity could contribute to the low number of newly approved drugs despite increasing investments in research and development. For synthetic organic chemists, it provides opportunities for exploring unconquered chemical space.[2] As illustrated by Lovering et al., in medicinal chemistry three-dimensionality and saturation are important factors for a successful transition from discovery through clinical trials to drugs.[3,4] In addition, the presence of stereogenic centers has positive effects.[5]

In light of the aforementioned analysis, we initiated a research program focusing on novel, three-dimensional heterocyclic scaffolds[6,7] with a high degree of complexity (as, for example, expressed by their Fsp^3).[8] Molecular diversity should result from substituents and the presence of suitable functional groups, which could be utilized in cross-coupling strategies.[9] The latter render the new compounds as ready-to-use building blocks applicable in automated parallel synthesis[10] and continuous flow.[11] Following this idea, we now introduce tricyclic heterocycles **1** (1,2,3,9b-tetrahydrobenzo[*c*]thieno[2,1-*e*]isothiazole 4-oxides), which to the best of our knowledge are unprecedented (Scheme 1). The synthetic route is flexible using readily available anilines **2** and tetrahydrothiophene (**3a**) as starting materials. Accordingly, various products have been prepared, and subsequent skeleton modifications led to functionalized building blocks for cross-coupling reactions.

Scheme 1. 1,2,3,9b-Tetrahydrobenzo[*c*]thieno[2,1-*e*]isothiazole 4-Oxides 1 and the Respective Starting Materials



The synthetic approach toward compounds **1** started by treatment of the respective aniline **2** with tetrahydrothiophene (**3a**), *N*-chlorosuccinimide (NCS), and triethylamine in DCM.[12] The resulting 2-(tetrahydrothiophen-2-yl)anilines **4** could generally be isolated in moderate to high yields ranging between 50% and 87% (Scheme 2). Neither the substitution pattern nor electronic effects of the aniline had a significant effect on the yields of **4**. Starting from *m*-iodoaniline, an almost 1:1 isomeric mixture of compounds **4l** and **4m** was obtained in a combined yield of 87%. The isomers were separated by flash column chromatography and were characterized individually. In addition, anilines with nitrogen atoms in the aromatic core reacted, providing **4o** and **4p** in 29% and 42% yield, respectively. All syntheses were carried out on a 60 mmol scale. Performing the reactions on a 250 mmol scale gave the products with essentially identical yields.

With the intention of expanding the substrate scope, 6-membered sulfur-containing heterocycles tetrahydro-2*H*-thiopyran (**3b**), *tert*-butyl thiomorpholine-4-carboxylate (**3c**), and 1,4-oxathiane (**3d**) were applied. To our delight, they reacted equally well, affording aniline-derived products **5a–c** in yields of 74, 80, and 72% yield, respectively (Scheme 2).[13]

Next, the direct conversion of 2-(tetrahydrothiophen-2-yl)anilines **4** into products **1** was targeted. Reacting **4** with NCS and NaOH resulted in cyclizations affording 1,2,3,9b-tetrahydro-4λ^4-benzo[*c*]thieno[2,1-*e*]isothiazoles **6** (Scheme 3). Without purification, products **6** were oxidized with *m*-CPBA to give tetrahydrobenzo[*c*]thieno[2,1-*e*]isothiazole 4-oxides **1**. In this manner, a wide range of products **1** bearing various functional groups was prepared. With the exception of naphthyl and pyrimidyl derivates **4n** and **4p**, all 2-(tetrahydrothiophen-2-yl)anilines **4** reacted well, affording the corresponding products **1** in yields ranging from 28% to 77% (Scheme 3). Also in this

Received: November 9, 2017

DOI: 10.1021/acs.orglett.7b03475
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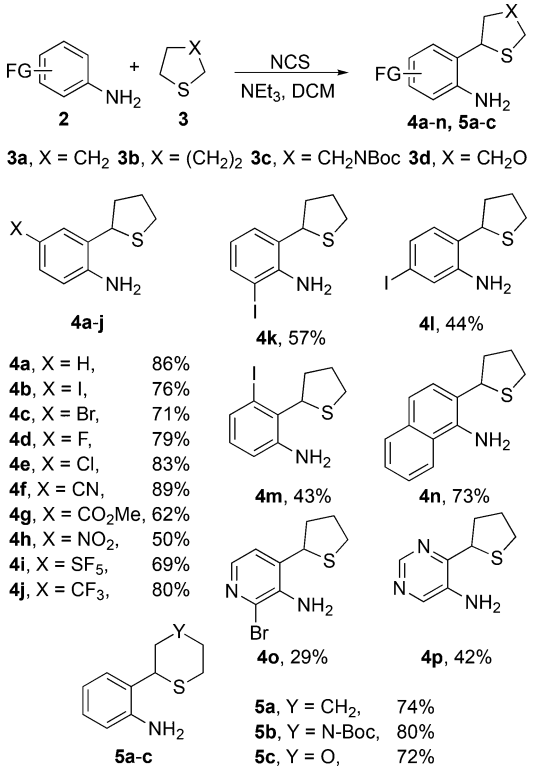
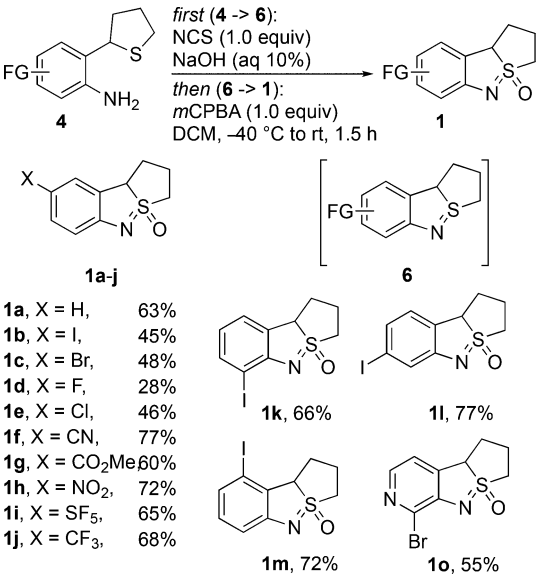
Scheme 2. Syntheses of 2-(Tetrahydrothiophen-2-yl)anilines 4a–p and Related Products 5a–c



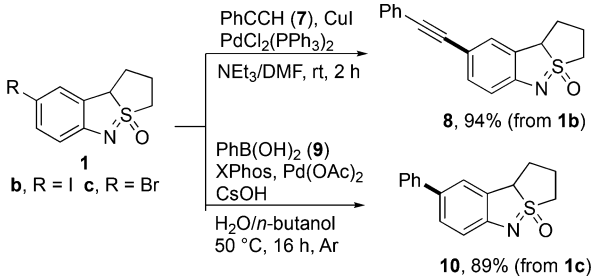
Scheme 3. Syntheses of Tetrahydrobenzo[*c*]thieno[2,1-*e*]isothiazole 4-Oxides 1



case, the reactions could be up-scaled, allowing the cyclization/oxidation sequence to be performed with up to 150 mmol of **4**. Attempts to apply **5a–c** under the same conditions remained unsuccessful.

In order to ensure that the heterocyclic core of products **1** allowed the application of metal-catalyzed cross-coupling strategies, compounds **1b** and **1c** were reacted with phenylacetylene (**7**) and phenylboronic acid (**9**), respectively, under palladium catalysis (Scheme 4). Both transformations proceeded well, giving alkynylated product **8** in 94% yield from the

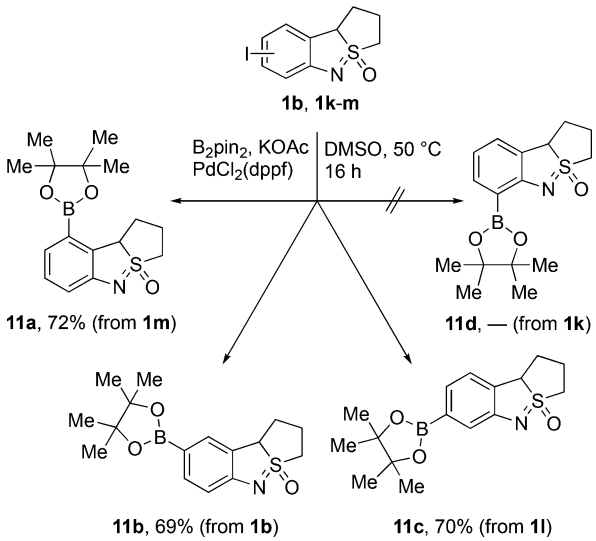
Scheme 4. Functionalization of Compounds 1b and 1c Using Cross-Coupling Strategies



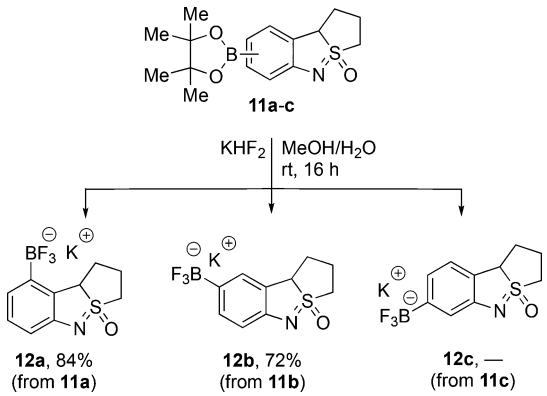
Sonogashira cross-coupling[14] and phenylated compound **10** in 89% yield from the Suzuki reaction.[15] Generally speaking, these modifications through cross-coupling reactions opened access to libraries of such heterocycles. As the reaction conditions were mild, sensitive coupling partners could be applied.

With the vision to incorporate three-dimensional heterocyclic scaffold **1** into bench stable, ready-to-use boron-based building blocks, pinacol boronic acid esters **11** and potassium aryltrifluoroborates **12** (Schemes 5 and 6) were targeted. Both

Scheme 5. Syntheses of Pinacol-Protected Boronic Acids 11a–c



Scheme 6. Syntheses of Potassium Aryltrifluoroborates 12a and 12b



DOI: 10.1021/acs.orglett.7b03475
Org. Lett. XXXX, XXX, XXX–XXX

reagent classes have proven highly valuable for Suzuki-type cross-coupling reactions.[15,16] Following a protocol described by Miyaura and co-workers, which involved the use of bis-(pinacolato)diboron (B_2pin_2), $PdCl_2$(dppf) (10 mol %), and potassium acetate in DMSO at 50 °C for 16 h,[17] pinacol boronic acid esters **11a–c** were readily prepared from the corresponding iodides (Scheme 5). Substitution at the C-6 position (with the intention to convert **1k** into **11d**) did not occur, either due to steric interactions of the heterocyclic backbone with the methyl groups of the pinacol fragment or chelating effects after palladium insertion into the aryl iodine bond.

Using a procedure introduced by Lloyd-Jones and co-workers,[18] potassium aryltrifluoroborates **12a** and **12b** were synthesized by treatment of pinacol boronic acid esters **11a** and **11b**, respectively, with KHF_2 in a methanol/water mixture for 16 h at room temperature (Scheme 6). Because of the high polarity of all compounds, the standard workup procedures could not be applied. Finally, the products were isolated and purified by washing with diethyl ether followed by repeated hot filtrations. In this manner, potassium aryltrifluoroborates **12a** and **12b** were obtained in yields of 84% and 72%. Attempts to prepare **12c** from **11c** failed. Although the product was detected by NMR spectroscopy, its isolation was hampered by its high polarity.

In summary, we developed a robust method for synthesizing three-dimensional heterocycles **1**. Sonogashira and Suzuki cross-couplings of halo derivatives allow straightforward structural modifications. Pinacol boronic acid esters and potassium aryltrifluoroborates with scaffolds derived from **1** represent bench stable, ready-to-use boron-based building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03475.

General experimental procedure and characterization details (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Laura Buglioni (formerly RWTH Aachen University, now ICIQ Tarragona), Stefan Wiezorek, and Dr. Christian Bohnen (both RWTH Aachen University) for helpful discussions during the project.

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DOI: 10.1021/acs.orglett.7b03475
Org. Lett. XXXX, XXX, XXX–XXX