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Benzo[*c*]isothiazole 2-Oxides: Three-Dimensional Heterocycles with Cross-Coupling and Functionalization Potential

Philip Lamers,[a] Laura Buglioni,[a] Steffen Koschmieder,[b] Nicolas Chatain,[b] and Carsten Bolm[a,*]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax: (+49)-241-809-2391; e-mail: Carsten.Bolm@oc.rwth-aachen.de
[b] Department of Hematology, Oncology, Hemostaseology, and Stem Cell Transplantation, Faculty of Medicine, RWTH Aachen University, Pauwelsstr. 30, 52074 Aachen, Germany

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Dedicated to Prof. Dr. Bernhard Lüscher on the occasion of his 60th birthday.

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Abstract: A robust method for the synthesis of benzo[*c*]isothiazole 2-oxides has been developed providing a range of functionalized derivatives starting from anilines and DMSO. The reaction sequence can be performed on a gram scale and leads to products that can easily be modified by standard cross-coupling reactions.

Keywords: benzo[*c*]isothiazole 2-oxides; cross-coupling; sulfur; synthetic methods

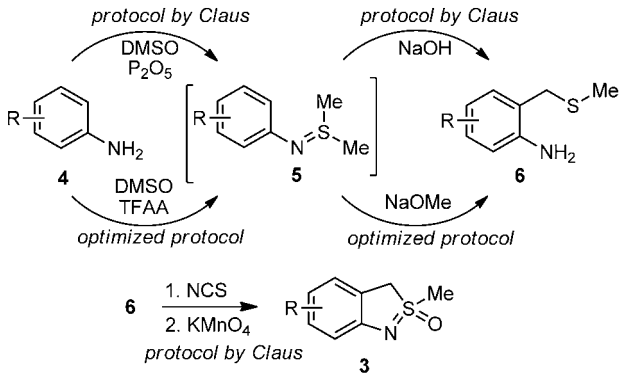
Heterocyclic architectures are key pillars for crop protection and medicinal chemistry.[1] The finding and development of new effective heterocyclic scaffolds has always been a major challenge for organic chemists.[2] In this context, the importance of nitrogen and sulfur has widely been documented.[3] Combining these elements in one functional group leads to sulfoximidoyl moieties, which are three-dimensional with the potential of having a stereogenic center at sulfur. Such increased complexity can impact on clinical success.[4] Following these arguments, compounds such as benzothiazines **1**,[5] benzisothiazol-3-one 1-oxides **2**[6] and related structures[7] have extensively been studied (Figure 1). To our surprise, 2-substituted 3*H*-2λ⁴-benzo[*c*]isothiazole 2-oxides **3** have received less attention, although a synthetic strategy was reported by Claus and co-workers as early as 1974.[8] Realizing that heterocycles **3** could be considered as three-dimensional bioisosteres[9] of oxindoles, which possess a high potential in medicinal chemistry,[10] we wondered about advancing the chemistry of such compounds by preparing a wider range of derivatives, including those allowing cross-coupling reactions for further derivatizations. The first results of these studies are presented here.

Initially, we planned to apply Claus's synthetic protocol (Scheme 1), which involved the *in situ* formation of dimethylsulfilimines **5** by treating mixtures of anilines **4** and DMSO with phosphorus pentoxide.[11] The subsequent addition of NaOH afforded benzyl methyl sulfides **6**.[12] Intramolecular oxidative sulfur imidations of **6** with NCS led to benzo[*c*]isothiazoles **7**, which were subsequently oxidized with $KMnO_4$ to give the desired compounds **3**.[8]

Figure 1. Examples of sulfur- and nitrogen-containing heterocycles.

Unfortunately, however, the reported reaction process proved difficult to reproduce und unreliable in the attempt to expand the substrate scope. Consequently, the approach had to be modified.

Inspired by the work of Jackson,[13] we decided to substitute P_2O_5 in the first step of the reaction sequence by trifluoroacetic anhydride (TFAA) (Scheme 1). Furthermore, NaOMe was used instead of NaOH for initiating the rearrangement from **5** to **6**. In this manner, the reproducibility problems were overcome, and a wide range of thiomethoxymethylated products **6** became accessible (Figure 2). Although the yields were only moderate to good due to incomplete conversions, the process proved reliable independent



Scheme 1. Synthetic approaches towards **3** *via* **5** and **6**.

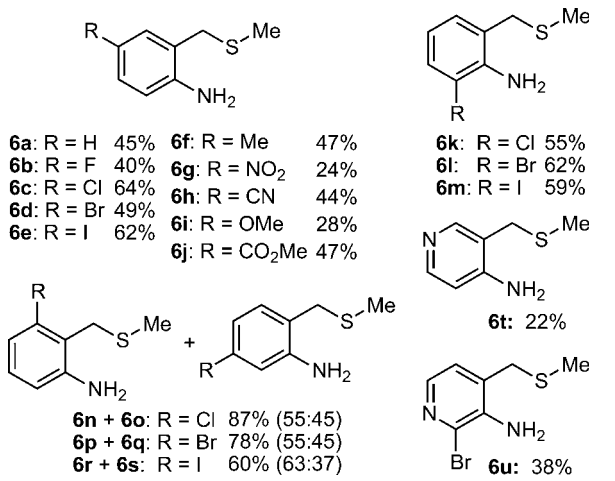
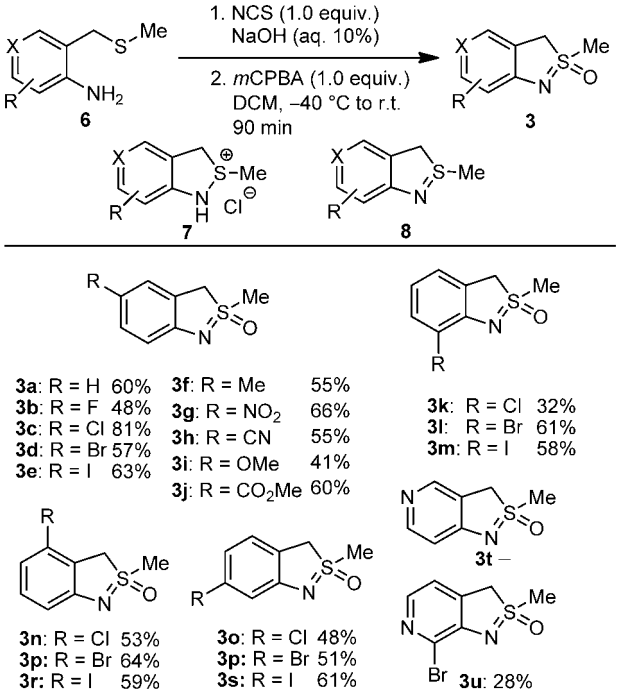


Figure 2. Products **6** prepared by the optimized protocol summarized in Scheme 1.

of the aniline substitution pattern. All reactions were performed on a gram scale employing approx. 150 mmol of the aniline derivatives. In the formation of the 1,2,4-trisubstituted products **6a–j** electronic effects induced by the substituents R appeared to be irrelevant. While single isomers of products **6k–m** were obtained starting from *ortho*-halo-substituted anilines, the analogous substrates with *meta*-substitution patterns led to mixtures of inseparable isomeric products (**6n/6o**, **6p/6q**, and **6r/6s**) with compositions ranging from 55:45 to 63:37. Finally, pyridine derivatives **6t** and **6u** were obtained in 22% and 38% yield, respectively.

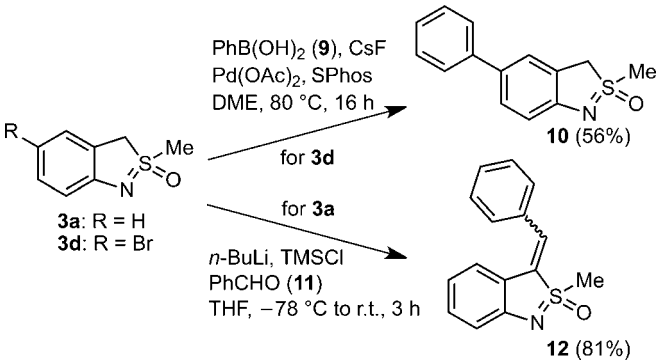
Next, we focused on the cyclization/oxidation sequence allowing the direct conversion of **6** into **3**. As in Claus's protocol,[8] NCS was used as reagent for the first step. Thus, treatment of **6** with 1.0 equiv. of NCS produced salts **7**, which upon addition of an aqueous solution of NaOH afforded benzo[*c*]isothiazoles **8**. Without further isolation, compounds **8** were directly oxidized to target products **3**. While the known procedure suggested the use of $KMnO_4$ for the last step,[8] *m*CPBA proved superior, allowing for the preparation of a broad range of products with various functional groups. With the exception of pyridine derivative **6t**, which led to a highly polar product that could neither be isolated by column chromatography nor by extraction from the aqueous phase, all thiomethoxymethylated anilines **6** reacted well, irrespective of the substitution pattern on the arene affording the corresponding benzo[*c*]isothiazole 2-oxides **3** in yields ranging from 28% to 81% (Scheme 2). Starting from the mixtures of **6n/6o**,



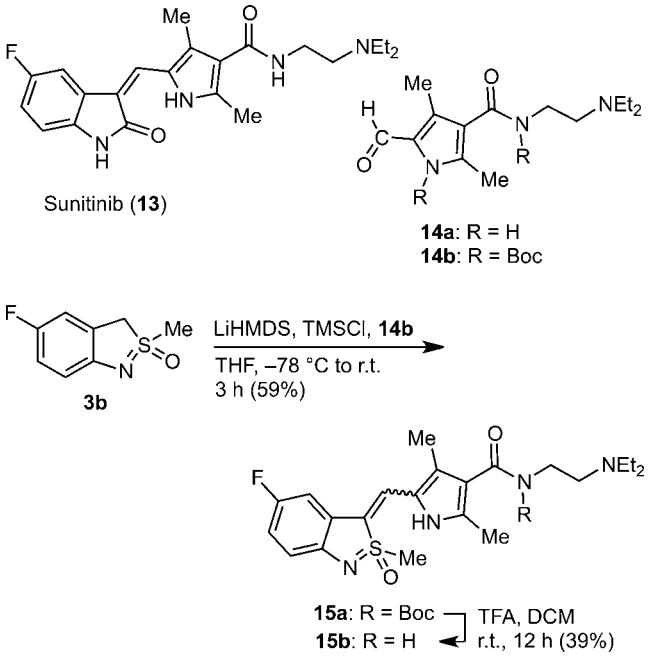
Scheme 2. Conversions of **6** into **3** under the optimized conditions.

6p/6q, and **6r/6s**, the resulting isomeric products **3n–s** could be separated and individually characterized. The yield of pyridine derivative **3u** was low (28%), but considering its high density of reactive positions, its formation was pleasing. Again, all of those transformations were performed on a gram scale using *ca.* 150 mmol of starting materials.[14]

Considering products **3** as structurally diverse molecular scaffolds with potential relevance for medicinal and crop protection chemistry, we next focused on exemplifying positional variability. Two routes were pursued (Scheme 3). First, a metal-catalyzed Suzuki-type cross-coupling was demonstrated using **3d** as representative starting material. Under conditions reported by Dughera, Ghigo and co-workers for the preparation of 7-arylsatines,[15] the



Scheme 3. Structural modifications of **3a** and **3d**.



Scheme 4. Sunitinib (**13**) and its analog **15b**.

palladium/SPhos-catalyzed reaction of **3d** with phenylboronic acid (**9**) in the presence of cesium fluoride afforded arylated benzo[*c*]isothiazole 2-oxides **10** in 56% yield.

The second approach made use of the acidity of the protons at position 3 of the heterocycle. Thus, deprotonation of **3a** with a combination of *n*-butyllithium (2.0 equiv.) and trimethylsilyl chloride (1.0 equiv.) followed by trapping of the resulting anion with benzaldehyde (**11**) led to olefinic product **12** (as an almost 1:1 mixture of diastereomers) in 81% yield.

Based on the idea that compounds **3** could mimic oxindoles we wondered about a bioisosteric replacement of the latter by the benzo[*c*]isothiazole 2-oxide fragment in a clinically relevant molecule. For pursuing this approach sunitinib (**13**),[16] an FDA approved tyrosine kinase inhibitor with potent antiangiogenic and antitumor activities, was taken as starting point (Scheme 4). Replacing the oxindole part of **13** by the respective heterocycle to give **15a** required the condensation of **3b** with aldehyde **14b**.[17] This transformation was achieved under the aforementioned reaction conditions (Scheme 3) with an alteration in base, which was changed from *n*-BuLi to LiHMDS. In this manner, **15a** was obtained with a 59% yield. Cleavage of the remaining Boc group by treatment with trifluoroacetic acid gave target compound **15b** in 39% yield (as 2:1 mixture of double bond isomers).

With **15b** available, we performed the first bioactivity study. The constitutively active tyrosine kinase receptor (RTK) FLT3-ITD is found in 25–30% of patients with acute myeloid leukemia[18] and is a target of sunitinib (**13**), reducing FLT3-ITD kinase activity.[19] We treated the murine pro-B-cell line (Ba/F3) stably expressing the oncogene FLT3-ITD, with increasing concentrations of **15b** and **13**. Cell viability was measured after 48 h of treatment. To our disappointment, **15b** proved inactive in this test. However, in the light of sunitinib's broad spectrum of effects on cellular processes, we continue to assume a high probability of finding enzyme-inhibitory activities by compounds such as **15b**.

In summary, we have developed an optimized procedure for the preparation of 2-methyl-substituted 3*H*-2λ^4-benzo[*c*]isothiazole 2-oxides,[20] which can be regarded as three-dimensional bioisosteres of oxindoles. Standard functionalizations of the core scaffold can be applied for molecular modifications, which might be of relevance for subsequent applications in medicinal and agricultural chemistry.

Experimental Section

General Two-Step Procedure for the Synthesis of 2-Methyl-3*H*-2λ^4-benzo[*c*]isothiazole 2-Oxides

Under an atmosphere of argon, DMSO (21.0 g, 19.1 mL, 270 mmol, 1.8 equiv.) was dissolved in a mixture of acetonitrile (50 mL) and DCM (50 mL). The reaction mixture was cooled to −78 °C and TFAA (37.5 g, 25.2 mL, 180 mmol, 1.2 equiv.) was added dropwise. The aniline (150 mmol, 1.0 equiv.) was dissolved in acetonitrile (50 mL) and added slowly to the solution. After stirring of the reaction mixture for 5 h at −78 °C, sodium methoxide (5.4 M in methanol, 19.1 mL, 450 mmol, 3.0 equiv.) was added dropwise over a period of 30 min at −78 °C. Then, the reaction mixture was allowed to warm up to room temperature and stirring was continued for 12 h. After addition of NaOH (300 mL, 2.8 M), the aqueous layer was extracted with DCM (3 × 350 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was then dissolved in acetonitrile (500 mL) and triethylamine (50 mL)

was added. After stirring for 16 h at 90 °C the solvent was removed under reduced pressure to afford product **6**, which was purified by silica gel column chromatography.

The resulting 2-[(methylthio)methyl]aniline (**6**, 15.0 mmol, 1.0 equiv.) was dissolved in DCM (50 mL) and the solution was cooled to −40 °C. A solution of NCS (2.03 g, 15.0 mmol, 1.0 equiv.) in DCM (50 mL) was added dropwise over a period of 60 min. After 15 min, an aqueous solution of sodium hydroxide (10%, 10 mL) was added and the reaction mixture was warmed to room temperature. After addition of water (100 mL), the organic layer was separated and cooled to −40 °C. Then, *m*CPBA (77% with water, 3.36 g, 15.0 mmol, 1.0 equiv.) was added in small portions over a period of 10 min. After 30 min the reaction mixture was allowed to warm to room temperature and sequentially washed with saturated aqueous solutions of Na_2SO_3 and $NaHCO_3$. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to afford product **3**, which was purified by silica gel column chromatography.

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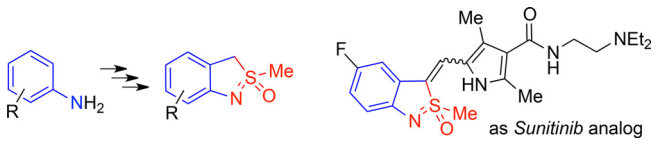
[20] With the vision of potential applications in medicinal and crop protection chemistry, the current approach only focused on the preparation of 2-methyl-substituted 3*H*-2λ^4-benzo[c]isothiazole-2-oxides. The development of preparative protocols towards products with other substituents will be part of future studies.

UPDATES

Benzo[*c*]isothiazole 2-Oxides: Three-Dimensional Heterocycles with Cross-Coupling and Functionalization Potential



Adv. Synth. Catal. **2016**, *358*, 1 – 6

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