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Accounting for Different Reactivities of Sulfinate and Thiosulfate Salts in Regioselective Azetidine Coupling via C-H Sulfenylation of Indoles

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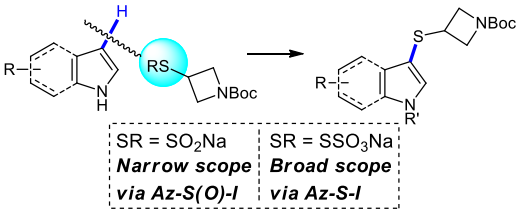

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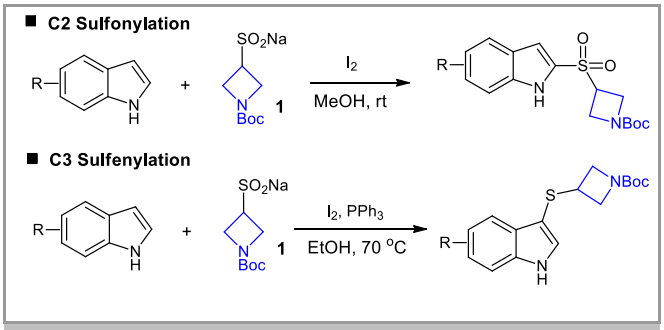
Abstract The regioselective incorporation of azetidines into heteroaromatic compounds is reported via a formal C-H sulfenylation reaction. While sodium sulfinate salts undergo C3 sulfenylation of electron rich indoles only, the corresponding thiosulfate salts have proved to be more generally useful. A mechanistic hypothesis for the different reactivities of sulfinate and thiosulfate salts is provided.

Key words Azetidine, coupling, indoles, C-H functionalization, thioether

The direct C-H functionalization of aromatic compounds has seen a recent surge in research activity and a range of C-C and C-heteroatom bond forming processes have now become well established.[1] One particularly effective application of this methodology is in its employment in the direct coupling of fragments that are of value to the fine chemicals industry. In this context, small ring heterocycles have been targeted as valuable molecules because of their attractive chemical and physical properties,[2] and this has inspired several approaches for the direct coupling of these fragments.[3] Our own interest in this field has led to the discovery of a C-S bond forming coupling of azetidine and oxetanesulfinate salts to indoles as a direct means of generating indole 2-sulfones.[4] More specifically, as shown in Scheme 1, the iodine promoted sulfonylation reaction developed by Deng and Kuhakarn[5] offered a convenient means for incorporating azetidines and oxetanes at C2. Preliminary studies suggested that a regiocomplementary process could be developed that delivered C3-substituted sulfides from the same starting materials, using the same authors' reductive coupling variant.[6] We report herein the scope and limitations of this process, and a mechanism driven hypothesis that has led to the discovery of thiosulfate (Bunte) salts as generally useful reagents for regioselective sulfenylation of indoles and pyrroles.

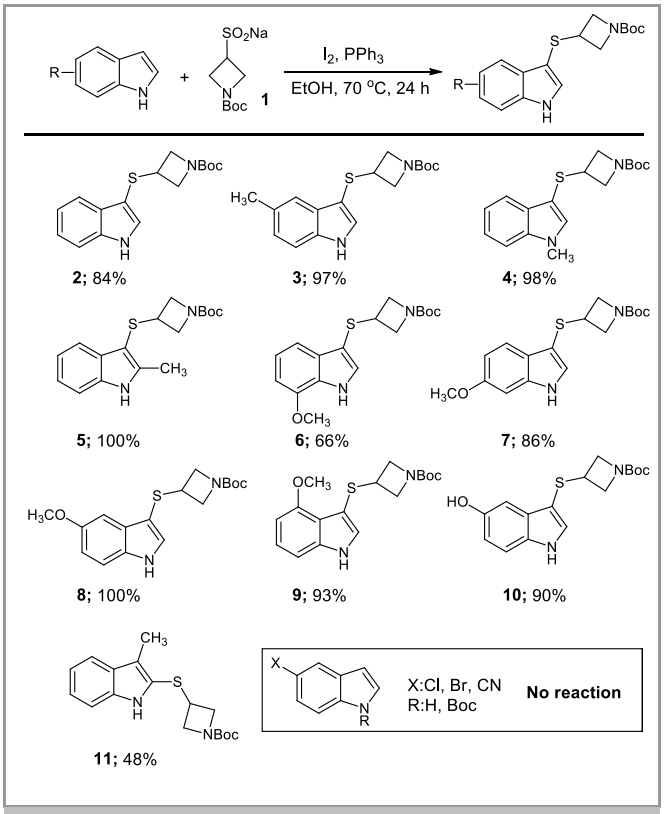


Scheme 1 Regiodivergent coupling for the introduction of azetidines into indoles.

We began our studies by exploring the generality of C3 sulfenylation of indoles using sodium sulfinate **1** in the presence of PPh_3 and iodine, and the scope is summarized in Scheme 2.

Coupling of the parent indole proceeded smoothly to generate **2** in high yield. Moreover, incorporation of a Me-group on the benzene moiety, indole nitrogen and C2-positions was well tolerated, providing **3-5** in excellent yield. We were also able to include a MeO-group at all positions on the arene ring, as well as a free phenol, giving azetidine sulfides **6-10**. Incorporation of a substituent at the indole C3-position resulted in a turnover of regioselectivity, providing **11** in modest yield. We next opted to explore indoles bearing electron withdrawing groups and were surprised to find that we were unable to observe any of the expected sulfides, and starting indole was recovered in each case (representative examples shown in Scheme 2).

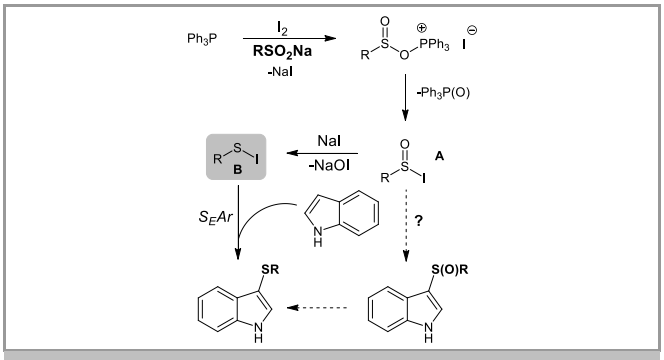
The proposed mechanism of the indole C3 sulfenylation involves the stepwise reduction of the sodium sulfinate salt to sulfenyl iodide B via the sulfoxinium iodide A (Scheme 3).[6] The reaction of sulfenium iodides and indoles is well established, and has been found to proceed efficiently with indole substrates bearing a range of electron rich/deficient groups.[7] The narrow scope



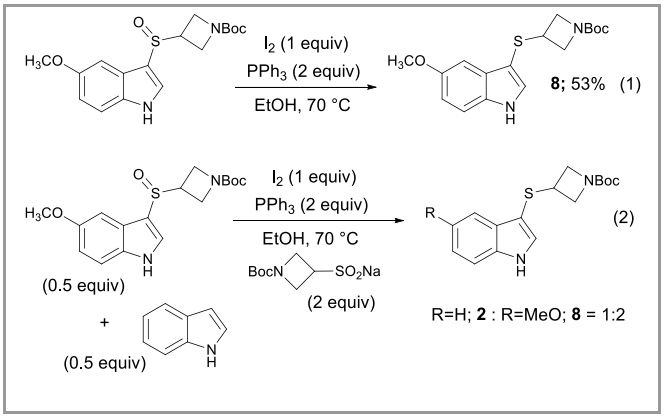
Scheme 2 C3 sulfenylation of indoles.

depicted in our results shown in Scheme 2 did not therefore appear to be consistent with this mechanism.

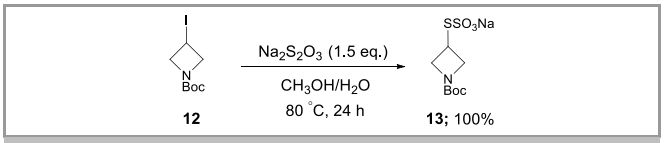
We speculated that the intermediate sulfinyl iodide **A**, if generated, would be an extremely reactive electrophile and wondered whether these intermediates were in fact involved in the C-S bond forming step. In order to investigate the veracity of this hypothesis, we prepared the corresponding sulfoxide of azetidine sulfide **8** and subjected it to iodine/PPh_3. As shown in Eq (1), the sulfoxide underwent reduction under these conditions to return **8** in modest yield. Moreover, subjecting an equal mixture of the same sulfoxide and indole to the reaction conditions generated both **2** and **8**. Moreover, during the preparation of this manuscript, Lu et al. showed that the PPh_3/NaI promoted trifluoromethylthiolation of indoles (via a putative sulfenium chloride) generated a sulfoxide by-product.[8] We believe therefore that a mechanism involving indole sulfoxide formation followed by reduction should be considered alongside the currently accepted sulfenyl iodide S_EAr pathway.



Scheme 3 Potential mechanisms of indole sulfenylation.

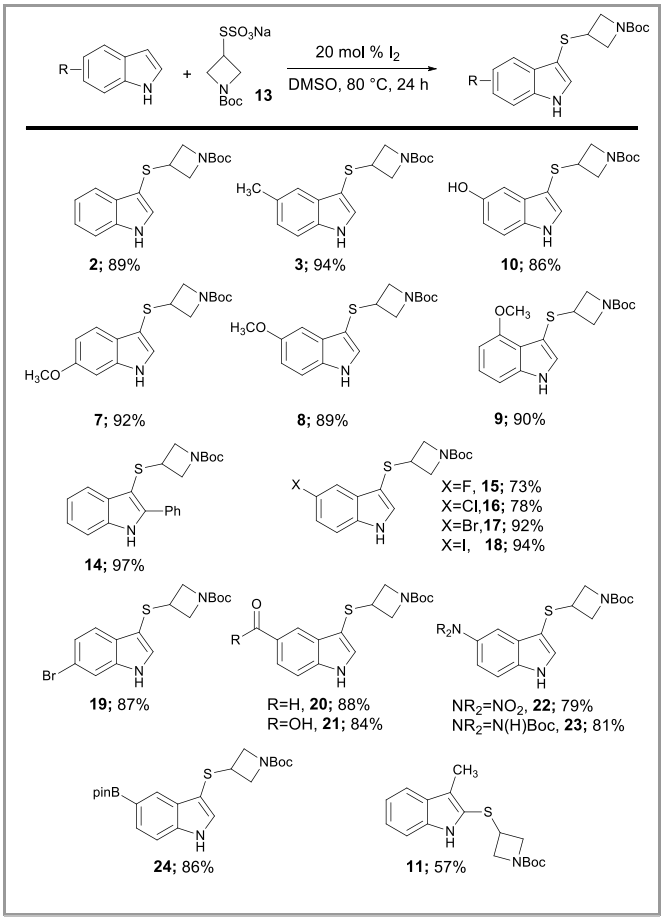


As the mechanistic studies suggested that the methodology depicted in Scheme 2 may not proceed through a sulfenium iodide intermediate, we decided to explore alternative means by which this electrophilic intermediate could be accessed. In this regard, Bunte salts represent a convenient source of sulfenium cations as they are readily prepared stable crystalline solids.[9] Moreover, Luo and Wang reported the elegant and pioneering use of these salts for the formation of indole 3-sulfides.[10] In order to investigate the potential of these salts as a vehicle for incorporating small ring heterocycles, we explored the preparation of the required azetidine thiosulfate salt (azetidine Bunte salt), our results are shown in Scheme 4. In the event, the addition of sodium thiosulfate to commercially available iodide **12** delivered the corresponding salt **13** in quantitative yield.



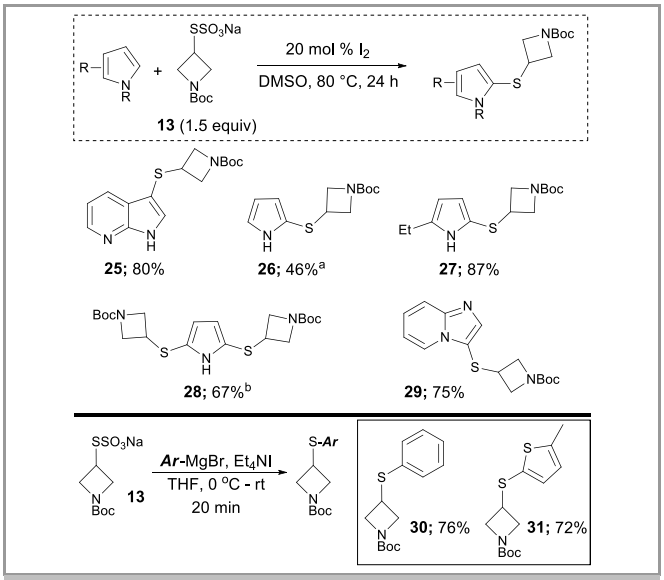
Scheme 4 Synthesis of azetidine Bunte salt **13**.

With the azetidine thiosulfate salt **13** in hand, we set about exploring the scope of the sulfenylation reaction using this compound, and our results are summarized in Scheme 5. We initially targeted the synthesis of a selection of indole azetidine sulfides prepared by the earlier sulfinate salt method (Scheme 2), and were pleased to find that this chemistry worked well providing compounds **2**, **3**, **7-10** and 2-Ph substituted indole **14** in high yield. Given the simple synthesis of precursor **13** in comparison to the corresponding sufinate salt **1**, this represents a very convenient method to access these compounds. We next turned our attention to substrate bearing a halide on the aryl ring that had proved to be unsuccessful in our earlier studies. The use of Bunte's salt **13** in this case delivered a series of halide substituted products **15-19** in excellent yield. In addition, the chemistry could be extended to previously unreactive electron deficient indoles, generating carbonyl derivatives **20**, **21**. Moreover, nitrogen containing substrates at the nitro- and amine-oxidation levels could be prepared with similar efficiencies (**22**, **23**). Finally, arylboronic esters were found to be compatible as were azaindoles, delivering functionalized scaffolds **24** in high yield. Overall therefore, we have found azetidine thiosulfate salt **13** to offer several advantages over the corresponding sulfinate salt **1**, including ease of synthesis and improved scope of reactivity.



Scheme 5 C3 sulfenylation of indoles using Bunte salt **13**.

Finally, we have been able to extend this method for the introduction of azetidines to other aromatic systems. As shown in Scheme 6, azaindole provided **25** in high yield, and pyrroles could undergo mono- and di-sulfenylation depending on reaction time and stoichiometry to give **26-28** with excellent regiocontrol. Moreover, we were able to couple azetidines to imidazo[1,2-a]pyridine to furnish **29** in excellent yield and regiocontrol. Reaction regiochemistry was confirmed in this case by X-ray crystallography.[11] Finally, we were also able to couple azetidines to less nucleophilic aromatic systems via the corresponding organometallic intermediates[12] as illustrated by the synthesis of benzene and thiophene bases azetidine thioethers **30** and **31**.



Scheme 6 Synthesis of azetidine thioethers of other aromatic systems. [a]Reaction stirred for 8 h. [b]3 Equiv of **13** used.

In conclusion, we report a simple method for the coupling of azetidines to indoles via sulfinate and thiosulfate salts, the latter appearing to show significantly broader scope. Although both salts have been proposed to function as reactive electrophiles through the intermediacy of a sulfenyl iodide, the significant differences in reactivities observed in their reaction with indoles has led us to propose that the sufinate salts react via an S_EAr reaction of an in situ generated sulfoxonium iodide.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(11) The supplementary crystallographic data for compounds **14**, **22** and **29** have been deposited with the Cambridge Crystallographic data Center as supplementary publication numbers CCDC 1534462, 1534463 and 1534461, respectively. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.CCDC.
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