



Cite this: DOI: 10.1039/c5cc00975h

Received 2nd February 2015,
Accepted 23rd February 2015

DOI: 10.1039/c5cc00975h

www.rsc.org/chemcomm

Synthesis and indole coupling reactions of azetidine and oxetane sulfinate salts†

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Azetidine and oxetane sulfinate salts are easily prepared from commercially available 3-iodoheterocycle precursors in a three-step sequence. They undergo smooth coupling reactions thereby providing an expedient route for the introduction of these four-membered heterocycles into indoles.

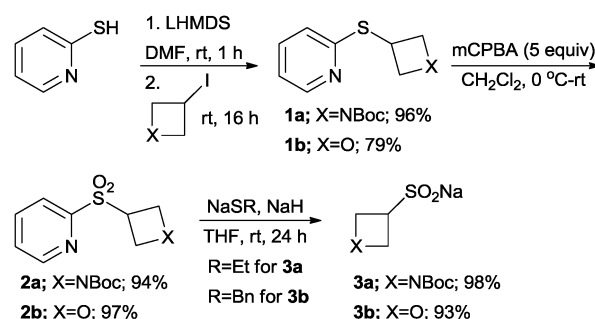
The direct incorporation of small strained sp³-rich heterocycles into a range of molecular scaffolds has recently received significant attention as these fragments have the potential to offer favourable pharmacological properties whilst contributing little to overall molecular weight.¹ In this regard, oxetanes have generated considerable interest in the medicinal chemistry sector because of their enhanced solubility and metabolic stability relative to traditional linkers such as carbonyl and *gem*-dimethyl moieties.² Azetidines are also of interest and have the added capacity to diversify *via* the N-atom.³ From a synthetic standpoint, the incorporation of azetidines and oxetanes into aromatic scaffolds by cross-coupling has been realized by the use of a number of transition metal catalysed processes. Negishi coupling of azetidin-3-ylzinc iodide was reported by Billotte, while more recently Rombouts and Molander have demonstrated the Ag-promoted coupling of azetidine and oxetane-derived trifluoroborates *via* the Minisci reaction.⁴ These small ring heterocycles can also be coupled as their corresponding alkyl halides *via* transition metal catalysis or the Minisci reaction.⁵ Finally, during the preparation of this manuscript, Baran reported a four step synthesis of azetidine sulfinate salts, and their subsequent employment in the direct alkylation of *N*-heteroaromatic compounds.⁶

Our own interests in this area have led to a cycloaddition strategy for the incorporation of oxetanes into *N*-heteroaromatic

compounds. Although this approach generated an intermediate that was amenable to further elaboration *via* cross-coupling, the synthetic route proved to be rather linear.⁷ The potential for direct incorporation of azetidines and oxetanes *via* cross-coupling seemed more attractive, and recent reports by Deng and Kuhakarn suggested that direct coupling *via* the use of a sulfone linker could offer an efficient means for achieving this goal.⁸ Moreover, this approach would complement sulfone promoted cyclisation and functionalization methodology developed by Bull and co-workers that allows 2-(aryl-sulfonyl)oxetanes to be accessed from chloromethyl arylsulfides.⁹

We began our studies by exploring the sulfonylation of indoles for which we required the corresponding 3-sulfinate salts of azetidine and oxetane, respectively. These compounds were accessed from the appropriate commercially available 3-iodo heterocycles in 3 steps and in good overall yield. Notably, we found the displacement of the pyridine group in the final step (2 → 3) to work well with sodium ethanethiolate, however, NaSBn was used in the synthesis of **3b** because of the easier removal of organosulfur by-products in this case. This process allowed the salts to be prepared on gram scale (see ESI†) (Scheme 1).

We found that azetidine sulfinate salt **3a** could be coupled to a range of indoles using the conditions reported by Kuhakarn (1.5 equiv. I₂, MeOH, rt) over a period of 24 h,^{8b} and the scope of this process is summarised in Scheme 2. Sulfonylation of indole

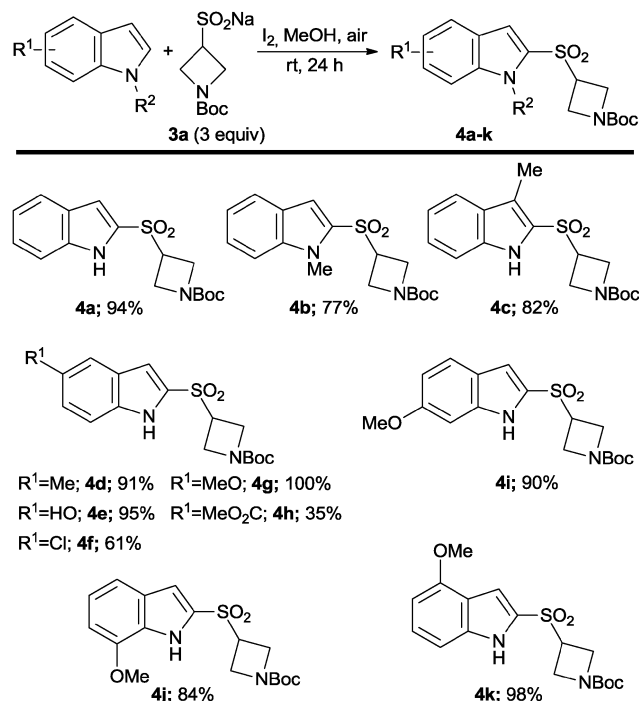


Scheme 1 Synthesis of azetidine and oxetane sulfinate salts.

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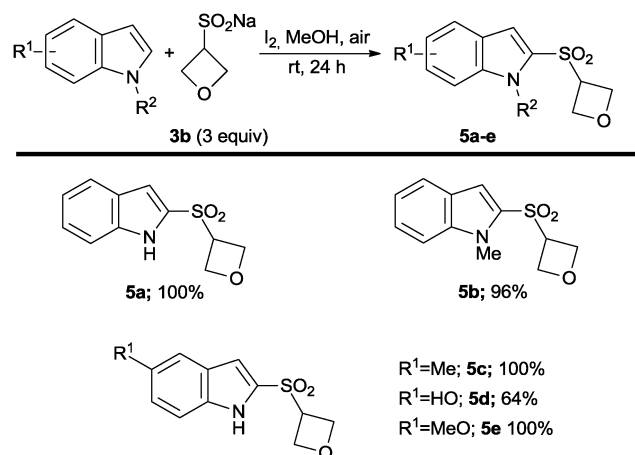
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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5cc00975h

Scheme 2 Sulfonylation of indoles using azetidine **3a**.

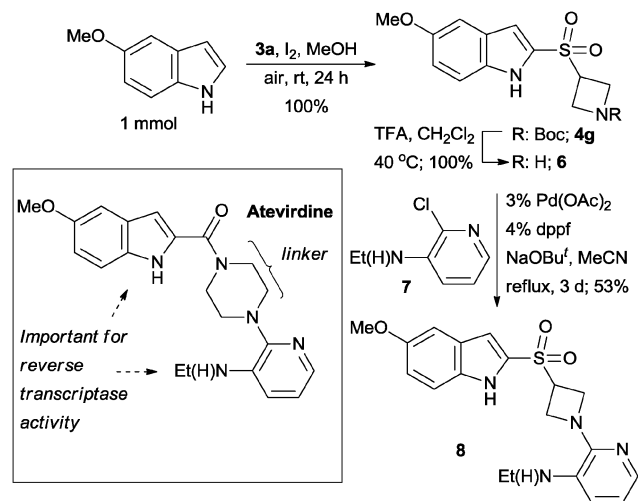
proceeded in excellent yield, and the coupling was found to be compatible with substrates bearing a methyl group at nitrogen and at the 3-position. A range of substituents were also tolerated at C-5, although the chemistry was more effective for indoles bearing electron donating groups (to give **4d,e,g**) relative to electron deficient analogues (**4f,h**). Finally, we found that the promoting effect of the MeO-group was effective at all positions on the fused benzene ring (**4g,i,j,k**).

We next explored the compatibility of this chemistry with the oxetane based sulfonate salt **3b** and our results are summarised in Scheme 3. We were pleased to find that the general trends highlighted in the case of the azetidine sulfonylation could be reproduced here. The reaction was found to work well with electron rich indoles, although the free hydroxyl was not as well tolerated in this case giving **5d** in relatively modest yield.

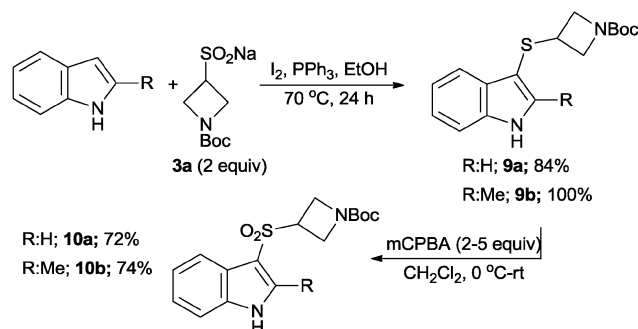
Scheme 3 Sulfonylation of indoles using oxetane **3b**.

As our objective was to introduce a versatile method for the direct introduction of small heterocyclic rings, we decided to employ this chemistry in the synthesis of an analogue of atevirdine, a reverse transcriptase inhibitor that has been studied for the treatment of HIV.¹⁰ As shown in Scheme 4, this compound consists of indole and pyridine moieties that modulate potency against reverse transcriptase. These fragments are linked by a piperazine spacer unit. We envisaged that replacing the acylpiperazine fragment with an azetidine sulfone would allow us to devise a short route to this class of compound that would permit the flexible variation of the key heteroaromatic fragments. Indeed, we found that **4g** could be prepared in near quantitative yield on 1 mmol scale, and that the Boc group could be smoothly cleaved by treatment with TFA. The amidation of 2-chloropyridine **7** proved to be quite challenging but we found that the use of dppf as a ligand provided product **8** in acceptable yield.¹¹ Hence a simple atevirdine analogue was rapidly assembled in a convergent route that offers the prospect for significant variation of both key heteroaromatic units.

Finally, we have found that the regioselective incorporation of small ring heterocycles at the C-3 position of indoles is also possible by employing a sulfonylation¹² followed by oxidation. This strategy allows access to regioisomeric analogues of azetidines **4** in good overall yield (Scheme 5).



Scheme 4 Synthesis of an atevirdine analogue.



Scheme 5 Sulfonylation of indoles followed by S-oxidation.

We report a convenient strategy for the direct incorporation of azetidines and oxetanes into indoles *via* the use of readily available sodium sulfinate salts. The reactions proceed under mild conditions, they are regioselective, and they allow access to C-2 or C-3 sulfone linked products. The potential of this chemistry for incorporation of the azetidines and oxetanes into other heterocycles is underway and will be reported in due course.

We are grateful to AstraZeneca and The University of Sheffield for financial support.

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