2-(Aryl-sulfonyl)oxetanes as designer 3-dimensional fragments for fragment screening: synthesis and strategies for functionalisation†

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2-Sulfonyl-oxetanes have been prepared, affording non-planar structures with desirable physicochemical properties for fragment based drug discovery. The oxetane motif was formed by an intramolecular C–C bond formation. The fragments were further functionalised via organo-metallic intermediates at the intact oxetane and aromatic rings.

Fragment based drug discovery (FBDD) is now a well-established approach in the development of new drugs and lead compounds.1 Fragments provide desirable starting points for discovery chemistry that allow increases in MW and lipophilicity during the optimisation of potency and selectivity,2,3 whilst remaining in drug-like chemical space.4 The design of fragment libraries is a crucial element to the success of screening. Although desirable criteria for properties of fragments can vary by biological target, guidelines for ‘fragment space’ proposed by Astex are widely cited (Rule-of-3: MW < 300, c log P ≤ 3, number of H-bond donors–acceptors ≤ 3).5 It has recently been suggested that the incorporation of more H-bond acceptors, up to 6, is advantageous in affording additional binding elements and further points for derivatisation during optimisation.6 Fragment screening samples a larger portion of available chemical space and as such FBDD is also a promising approach for complex and challenging targets such as protein–protein interactions.7 Fragment libraries dominated by sp2-rich molecules have been less successful in generating hits for these targets, suggesting more ‘3-dimensional’ fragments are likely to be required.8 Indeed, more sp3-rich molecules and aliphatic heterocycles can offer improved levels of success through development, relative to highly aromatic compounds.9,10

Oxetanes have recently been highlighted as desirable low molecular weight motifs for drug discovery.11 Carreira, Rogers-Evans, Müller, and coworkers have shown an oxetane motif can act as an isosteric, polar replacement for a gem-dimethyl group or a carbonyl, which can result in improved physicochemical and biochemical properties relative to the parent molecule.12 Enhanced solubility, reduced lipophilicity, reduced hERG liability as well as improved metabolic stability were observed as potential beneficial effects. The oxetane motif is also found in several biologically active natural products, such as oxetanocin, taxol and mitrophorone.13 As a result, oxetanes have recently received significant interest in medicinal chemistry.14

We are interested in the preparation of novel non-planar fragments, with desirable properties, which contain biologically important motifs, and access new areas of chemical space.15 Consequently we designed 2-sulfonyl oxetanes (Fig. 1), as non-planar fragments to comply with the rule-of-3, modified for the number of hydrogen bond acceptors (HBA).16 We envisaged that these small and functional group rich molecules, with the potential to make interesting interactions, would be desirable fragments for screening in drug discovery or chemical biology programmes. In addition they would allow the structure to be ‘grown’ or ‘linked’ in several directions for optimisation, were they to be a hit. Here we report the synthesis of sulfonyl oxetanes as well as their further functionalization.

The synthesis of oxetanes remains a challenge. Methods for the synthesis of oxetanes are mostly limited to two general approaches: photochemical Paternó–Büchi [2+2] reactions of carbonyl compounds with alkenes,17 or intramolecular Williamson etherification (Fig. 2).11,18 Recently epoxide ring opening/ring closing has been exploited as a facile route to the activated intermediate.

![Fig. 1 Sulfonyl-oxetane targets. MW = molecular weight; c log P = calculated log P (lipophilicity); HAC = heavy atom count (number of non-H atoms); HBD/A = number of hydrogen bond donors–acceptors.](image-url)
that undergoes etherification.\textsuperscript{19} Substituted oxetanes have also been generated from \textit{exo}-methylene oxetanes.\textsuperscript{20} However, these approaches are unsuitable for our targets, particularly due to the instability of the often required \textit{exo}-sulfonyl oxo-anion intermediate.\textsuperscript{21}

To incorporate the 2-sulfonyl group, we envisaged a strategy involving C–C bond formation, as opposed to the usual C–O bond formation (Fig. 2, lower). While this approach is necessitated in ring closure to form cyclobutanes and is known in the synthesis of azetidines,\textsuperscript{22} it has not been exploited for oxetane synthesis. For oxetanes, a comparable mode of cyclisation has only been observed in intramolecular epoxide opening of lithiated benzyl ethers, using LDA-KO\textsubscript{t}Bu at \textminus78 °C.\textsuperscript{23,24}

The route developed to sulfonyl-oxetanes 1\textit{a–d} is shown in Scheme 1. The cyclisation precursors were accessed by alkylation of ethylene glycol with chloromethyl aryl-sulfide to afford S,O-acetal 3, using ethylene glycol as solvent to avoid double alkylation. Tosylation\textsuperscript{25} followed by oxidation with 3,4,6-trichloro-1,2-benzisothiazole 5 (T\textsubscript{m}B)

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Finally we examined the cross-coupling of sulfonyl oxetane 1c from the aryl chloride. The chloride substituent provides an interesting potential binding element and also provides a route to further derivatisation to access allyl and aryl derivatives. Fürstner recently reported an iron-catalysed cross-coupling of Grignard reagents with aryl chlorides. Employing Fürstner’s conditions with 1c afforded oxetanes 11 and 12 in good yields. Hexylmagnesium bromide and propylmagnesium chloride were successfully cross-coupled, in the presence of the acidic α-sulfonated oxetane proton, and without noticeable ring opening of the oxetane (Scheme 3, conditions a).

Suzuki cross-couplings of chloride 1c with boronic acids were also successful using Buchwald’s SPhos ligand with Pd-catalysis (Scheme 3, b). Electron-rich and electron-poor aromatic boronic acids were successful, affording oxetanes 13–16.

In summary, here we report a new approach to the synthesis of 2-functionalised oxetanes that provides novel fragment-like compounds. The initial fragments can be further elaborated through lithiation on the oxetane ring itself, by directed ortho-meta-limited on the aromatic, as well as by iron and palladium catalysed cross-couplings of the aryl chloride. We are currently expanding the diversity of small ring fragments that can be obtained by this approach and developing enantioselective routes.

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Notes and reference

3 M. M. Hann, MedChemComm, 2011, 2, 349.

16 See ESIF for calculated molecular properties of all oxetane derivatives and energy-minimised structures of oxetanes 1a and 5 to indicate 3D shape.
26 See ESIF for details of reaction optimisation.