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1,6-Dioxo-2-azaspiro[3.4]oct-2-enes and Related Spirocycles: Heterocycles from [3+2] Nitrile Oxide Cycloadditions with 2-Methyleneoxetanes, -Thietanes, and -Azetidines

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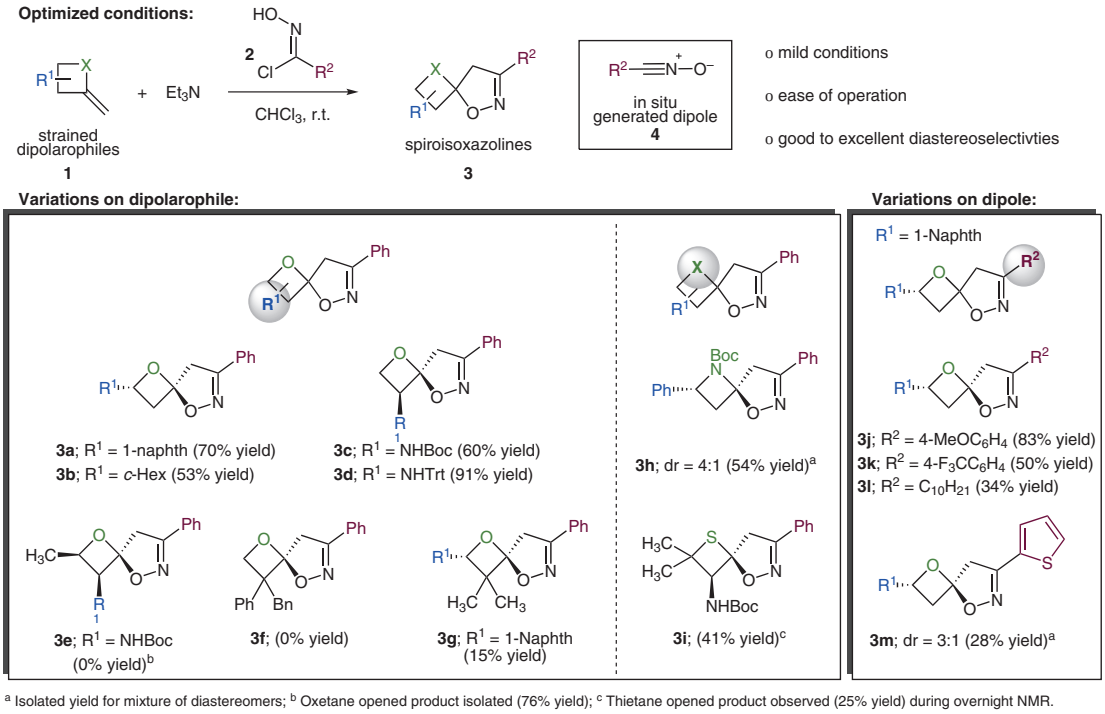
Strained *exo*-Methylene Heterocycles as Dipolarophiles: Synthesis of Unexplored Spiroisoxazolines



[a] Isolated yield for mixture of diastereomers; [b] Oxetane opened product isolated (76% yield); [c] Thietane opened product observed (25% yield) during overnight NMR.

Significance: Spiroheterocycles have been of significant interest in medicinal chemistry due to their non-planar topology (M. Rogers-Evans et al. *Chimia* **2014**, *68*, 492) and there have been considerable efforts towards the synthesis of these compounds. Syntheses of spirocycles with four-membered heterocycles such as spirooxetane and spiroazetidine pose additional challenges, as these rings are more strained than their five- or six-membered counterparts. However, their compactness and three-dimensional properties make them desirable scaffolds in drug discovery. The current report details a regio- and diastereoselective [3+2] cycloaddition of strained alkenes **1** and nitrile oxides **4** to provide previously unreported spiroisoxazolines **3** bearing four-membered oxetanes, azetidines and thietanes.

Comment: The authors report that when the precursor to nitrile oxide **2** was added slowly to the dipolarophile **1** and base, improved yields were observed. A variety of aliphatic, aromatic and N-substituents on the 2- and 3-positions of the heterocycle were tolerated (**3a–d**). In contrast, 3,3-bis-substituted 2-methylene oxetanes gave lower yield (**3g**) or no product (**3f**). Azetidine and thiophene dipolarophiles gave moderate yields of the spiroisoxazolines (**3h–i**). Different aromatic and aliphatic groups were tolerated on the dipole precursor (**3j–m**). In certain cases, the desired isoxazolines were converted into ring-opened products either readily (**3e**) or over time (**3i**). Further studies on the stability and reactivity of these compounds would help to expand the scope and applications of these heterocycles.

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