Synthesis of Novel *N*-Heterocyclic Scaffolds for Combinatorial Chemistry

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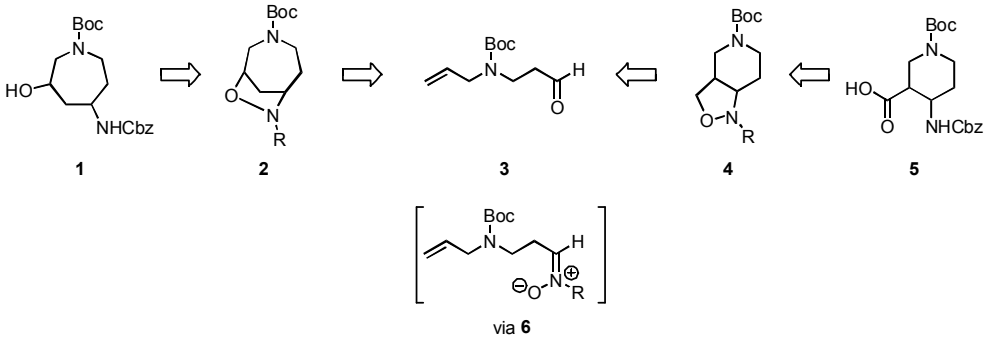
In the course of our studies towards new scaffolds for combinatorial chemistry, we investigated the formation of functionalized *N*-heterocycles with intramolecular 1,3-dipolar cycloadditions as the key step. Along these lines, a twofold protected azepanol scaffold as well as a protected piperidine derived amino acid could be obtained from a common aldehyde in short and scalable syntheses.

Different Products of Intramolecular Cycloadditions

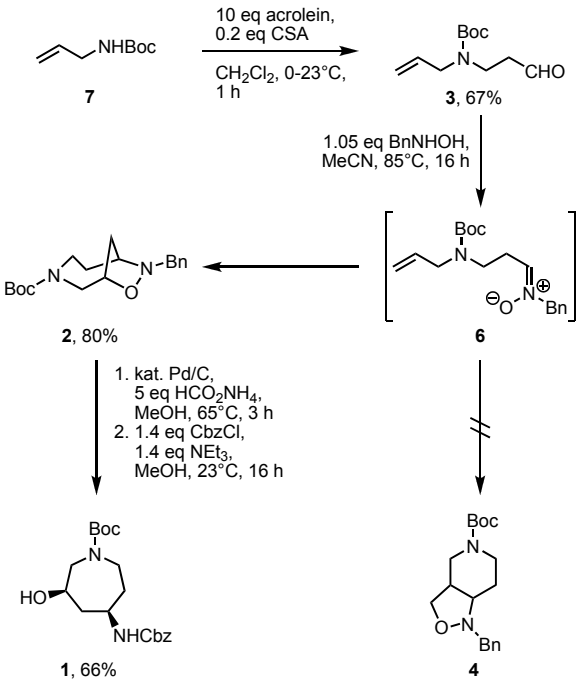


1 **2** **3** **4** **5**

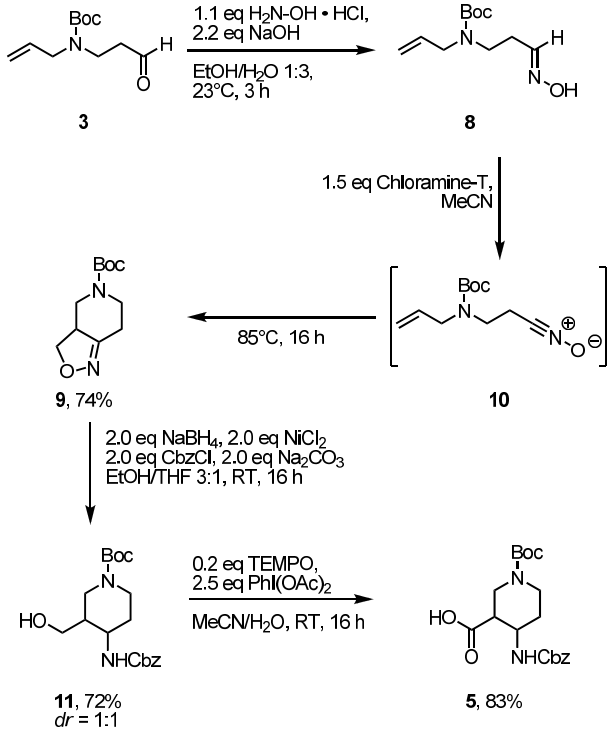
The intramolecular 1,3-dipolar cycloaddition of the nitrone **6** which can be obtained from the aldehyde **3** can result in two different regioisomeric isoxazolines. Depending on the cyclisation mode (*endo* or *exo*) the bridged azepane **2** and the fused piperidine-derivative **4** are possible. These isoxazolines can be further converted into interesting scaffolds, namely the azepanol **1** and the amino acid **5**.

Synthesis of the Orthogonally Protected Azepanol

The common intermediate aldehyde **3** can be obtained by reaction of *N*-protected allylamine **7** with an excess of acrolein in 67%. Reaction with *N*-Benzylhydroxylamine gives the nitrone **6** which is not isolated. Interestingly, after the cycloaddition only the electronically favoured azepane **2** was obtained in good yield, whereas the piperidine **4** could not be detected. Reduction of the N-O bond via transfer hydrogenation with ammonium formate and subsequent protection of the amino group with CbzCl gave the twofold protected scaffold **1** in 66% yield.[1]



Synthesis of Piperidine Derivatives



In order to obtain the regioisomeric alcohol **11**, the route was slightly modified. The aldehyde **3** was converted into the nitrile oxide **10** instead of the nitrone **6** in two steps using Chloramine-T in order to oxidize the intermediate oxime **8**. Due to steric reasons the isoxazoline **9** is the only product formed in the following cycloaddition. The reduction of the isoxazoline ring and the protection of the amino group with CbzCl could be achieved in one step, using a $NiCl_2$-$NaBH_4$ reduction. The product was obtained as a 1:1 mixture of diastereomers. The formed alcohol **11** was directly transformed into the corresponding acid using TEMPO as catalyst and $PhI(OAc)_2$ as the oxidant. At this stage the diastereomers could be separated using column chromatography giving access to the *cis*- and *trans*-amino acid **5**.

[1] M. Würdemann, J. Christoffers, *Synlett* **2011**, 2841-2843.