Synthesis of New 1,4-Diazocines as Scaffolds for Combinatorial Chemistry

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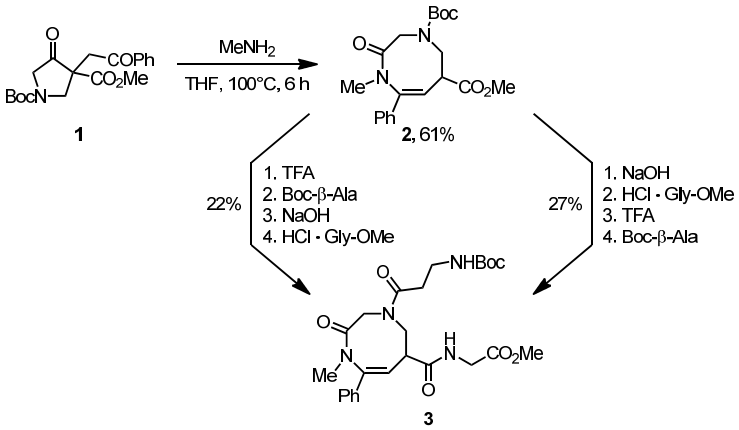
We report on the synthesis of new 1,4-diazocine-6-carboxylic acids which define cyclic β-alanine derivatives including a conformationally rigid scaffold. Those compounds can be integrated into peptide chains due to orthogonally protected functional groups. Furthermore, 1,4-diazocines can be used as scaffolds for combinatorial library synthesis.

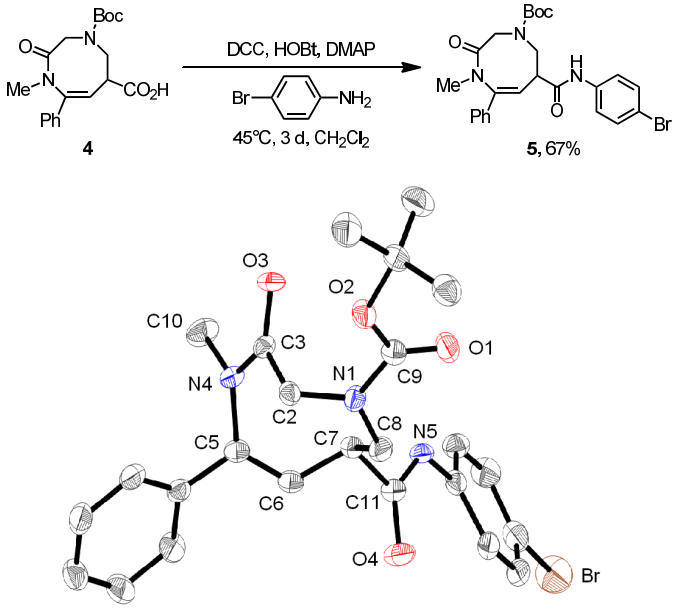
Preparation of Methyl 1,4-Diazocine-6-carboxylate

The formation of the eight-membered ring **2** proceeded with methylamine *via* a retro-*Claisen*-reaction.[1] After deprotections with NaOH or TFA, respectively, and amidations according to standard protocol with DCC-HOBt-DMAP, tripeptoidic structure **3** was synthesized along two alternative routes.



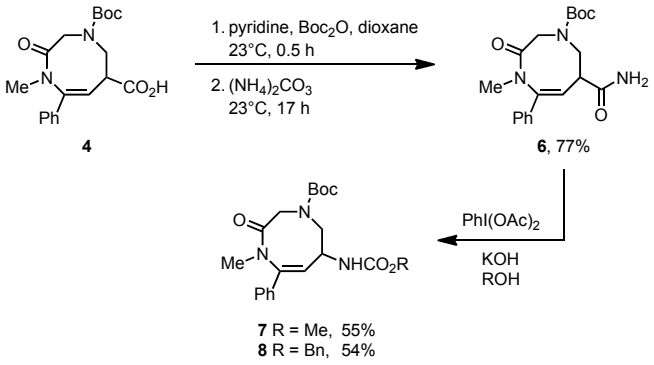
X-Ray Crystallography of the Eight-Membered Ring

Carboxylic acid **4** was coupled with 4-bromoaniline to give amide **5**, which showed good crystallinity. X-Ray analysis indicated that the eight-membered ring is in a folded, crown shaped conformation.



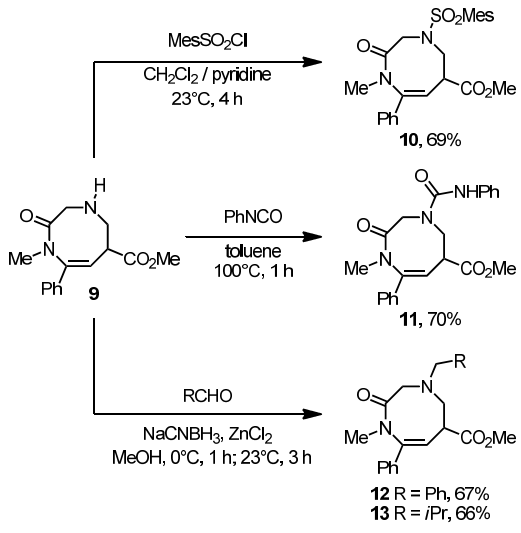
Degradation of the Carboxylic Function

Our intention to synthesize the 6-amino derivative of the diazocine scaffold was carried out by preparing the unsubstituted amide **6** first. A variant of a *Hofmann*-type degradation with use of $PhI(OAc)_2$ and MeOH or BnOH, respectively, was fruitful to yield the protected amines **7** and **8**.



Synthesis of further 1,4-Diazocine Derivatives

Additionally, 1,4-diazocine **9** was derivatized with different reagents at N-1 to show its suitability as a scaffold for combinatorial chemistry. Therefore, amidation with mesitylensulfonylchloride gave sulfonamide **10**. Urea **11** was prepared by coupling amine **9** and phenylisocyanate. Reductive amination in presence of $NaCNBH_3$ and Lewis acid $ZnCl_2$ with either benzaldehyde or isobutyraldehyde gave the amines **12** and **13**.



Conclusions

- 1,4-Diazocine was synthesized as a new scaffold and could be integrated into a tripeptoidic structure.
- The folded conformation could be established *via* X-Ray analysis.
- Further diversifying transformations were performed.

[1] M. Penning, J. Christoffers, *Eur. J. Org. Chem.* **2012**, 1809-1818.