SYNTHESIS OF 1,2-DIAZETIDIN-3-ONES VIA THE UGI REACTION COMPRISING α-HYDRAZINO ACIDS

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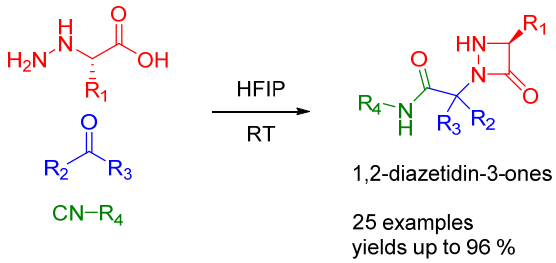
Heterocyclic compounds constitute the largest and probably the most studied class of organic compounds, owing to their ubiquity in Nature and myriad of manifested activities. Four-membered rings are particularly attractive scaffolds, owing to their ability to adopt, upon functionalization, a distinct 3D structure, a highly desirable feature in drug discovery process. Among nitrogen-containing heterocyclic rings, 1,2-diazetidin-3-ones (aza-β-lactams) emerged as pharmaceutically promising motifs, upon the discovery that they act as potent inhibitors of the serine hydrolase protein phosphatase methylesterase-1.

Available methods for the synthesis 1,2-diazetidin-3-ones rely on [2+2] cycloaddition of a ketene with an azo compound [1] or intramolecular ring cyclization chemistry, like recently reported intramolecular N-H insertion reaction of rhodium carbene intermediates derived from diazocarbonyl compounds [2]. Here we report a smooth access to a library of chiral N^{β}-substituted 1,2-diazetidin-3-ones utilizing a three-component Ugi reaction. α-Hydrazino acids were used as bifunctional components with various carbonyl and isocyano-components to afford 1,2-diazetidin-3-ones in yields up to 96 %. Post-condensation modifications were also probed to introduce additional structural complexity.



Scheme 1. 3C-Ugi reaction affording 1,2-diazetidin-3-ones

[1] J. M. Berlin, G. C. Fu, *Angew. Chem. Int. Ed.* 2008, 47, 7048–7050.

[2] M. S. Santos, A. Nortcliffe, W. Lewis, T. D. Bradshaw, C. J. Moody, *Chem. Eur. J.* 2018, 24, 8325–8330.