Stereoselective synthesis of *cis*-3,4-disubstituted piperidines through ring transformation of 2-(2-bromo-1,1-dimethylethyl)azetidines and 2-(2-mesyloxyethyl)azetidines

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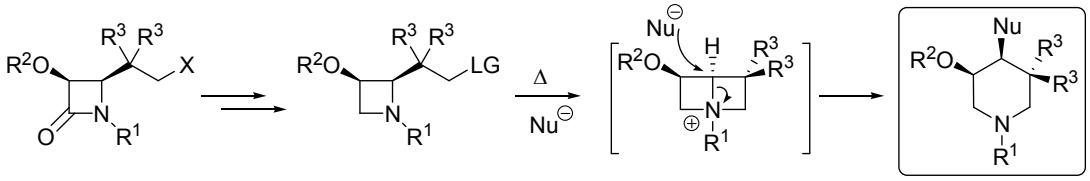
Within azaheterocyclic chemistry, azetidines are an extraordinary class of strained compounds, which makes them excellent candidates for nucleophilic ring-opening or ring-expansion reactions yielding highly substituted acyclic amines or higher ring systems.
In this presentation, the reactivity of 2-(2-bromo-1,1-dimethylethyl)azetidines and 2-(2-mesyloxyethyl)azetidines, obtained through monochloroalane reduction of the corresponding β-lactams, with regard to different nucleophiles is evaluated for the first time, resulting in the stereoselective preparation of a variety of new 4-acetoxy-, 4-hydroxy-, 4-bromo-, 4-formyloxy- and 4-fluoropiperidines.[1,2] Piperidines are found in a whole variety of natural products and pharmaceutical compounds, and they continue to attract considerable attention due to their diverse and important biological activities.



R^1 = allyl, *t*Bu, *i*Pr, *c*Hex
R^2 = Bn, Ph
R^3 = H, Me
X = OTBDMS, Br

LG = Br, OMs

Nu = OAc, OH, Br, OCOH, F

During these reactions, transient 1-azoniabicyclo[2.2.0]hexanes were prone to undergo an S_N2-type ring opening to afford the final azaheterocycles. Furthermore, *cis*-4-bromo-3-(phenoxy- or benzyloxy)piperidines were elaborated into the piperidin-3-one framework via dehydrobromination followed by acid hydrolysis. Finally, a new protocol for the ring expansion-oxidation of the starting azetidines into piperidin-4-ones was developed.

References

[1] K. Mollet, S. Catak, M. Waroquier, V. Van Speybroeck, M. D'hooghe, N. De Kimpe, *J. Org. Chem.* **2011**, *76*, 8364-8375.
[2] K. Mollet, L. Broeckx, M. D'hooghe, N. De Kimpe, *Heterocycles* **2012**, *84*, 431-447.