SELECTIVE TRANSFORMATION OF 2-BROMOMETHYL-2-METHYLAZIRIDINES TO FUNCTIONALIZED AZIRIDINES AND AZETIDINES

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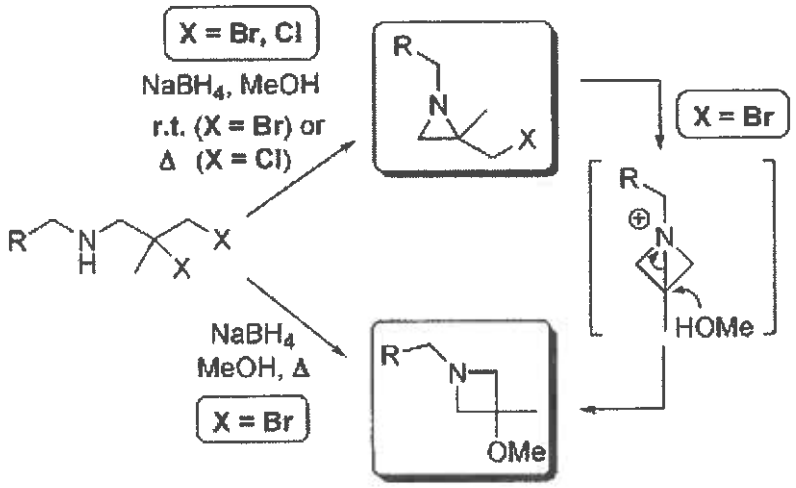
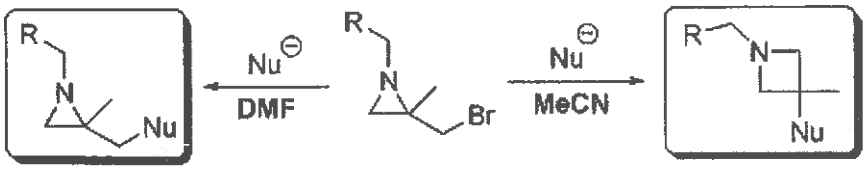
Within azaheterocyclic chemistry, aziridines and azetidines are extraordinary classes of strained compounds with diverse applications.

In this work, β,γ-dihalogenated amines, prepared by reduction of the corresponding dihalogenated imines, were shown to be good substrates for the selective synthesis of 2-halomethyl-2-methylaziridines and 3-methoxy-3-methylazetidines depending on the reaction conditions. When β,γ-dichlorinated amines (X = Cl) were treated with $NaBH_4$ in methanol under reflux, only the corresponding aziridines were obtained. On the other hand, the analogous β,γ-dibrominated amines (X = Br) furnished 3-methoxy-3-methylazetidines under the same conditions. The ring transformation to azetidines was explained by the ring expansion of kinetically favored 2-bromomethyl-2-methylaziridines, obtained by the reaction of the dibrominated amines with $NaBH_4$ at room temperature. This peculiar aziridine to azetidine rearrangement was shown to be mediated by the formation of bicyclic aziridinium species, which were subsequently opened at the more hindered position by methanol.



Whereas 2-chloromethyl-2-methylaziridines were shown to be highly reluctant to further derivatization, the reactivity of 2-bromomethyl-2-methylaziridines with regard to different nucleophiles was further investigated, providing an efficient strategy toward the selective synthesis of a large variety of functionalized aziridines and azetidines. The reaction outcome was proven to be controlled by the nature of the solvent, showing DMF to be a suitable solvent for the synthesis of the corresponding aziridines and MeCN for the synthesis of the corresponding azetidines via strained bicyclic intermediates.



Nu = CN, OAc, OPh, SCN...

References

Stanković, S.; Catak, S.; D'hooghe, M.; Goossens, H.; Abbaspour Tehrani, K.; Bogaert, P.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N. J. Org. Chem. 2011, 76, 2157.