A new method for the synthesis of pyrazolidines

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A new method for the synthesis of pyrazolidines.

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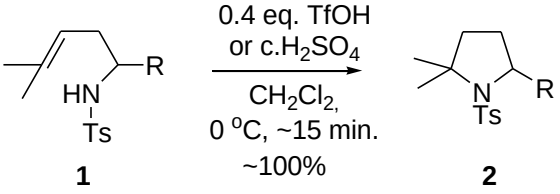
Abstract- Fully protected pyrazolidines can be readily obtained by acid-catalysed cyclisations of the corresponding allylic hydrazines by carbenium ion generation using concentrated sulfuric acid in dichloromethane.

Key words: Pyrazolidine; synthesis; acid-catalysed; cyclisation; hydrazines.

Pyrazoles and their partly and fully reduced derivatives, pyrazolines and pyrazolidines, form an important group of heterocycles, with potentially important contributions to make to drug design by reason of their ability to form strong hydrogen bonds at either or both nitrogen atoms. It is perhaps also significant that Nature does not seem able to form N-N bonds directly and hence such compounds will occupy an entirely non-natural portion of chemical space and hence are likely to continue to play a central role in the discovery of novel pharmaceuticals.[2] Despite the enormous contribution made by heteroaromatic residues, both with and without incorporated nitrogen atoms in a majority of commercial drug structures, it has recently become plain that to achieve a continuation of this success, it would be wise to embrace semi-saturated and fully saturated analogues of such structural features, in order to introduce both greater flexibility and increased three dimensional shape.[2]

Many synthetic routes have been defined for the syntheses of such heterocyclic systems, but quite often these suffer from a lack of regioselectivity, particularly when both C-N bonds are formed effectively simultaneously from a hydrazine and an all-carbon *bis*-electrophile such as a 1,3-dicarbonyl or a conjugated enone.[3] Hence, often it is preferable to assemble such structures using a stepwise approach.[4,5] The inspiration for the present methodology was derived from a possible extension of our finding that unsaturated sulfonamides **1** are readily converted into the corresponding pyrrolidines **2** following exposure to acid,[6] in an intramolecular hydroamination reaction. A particularly rapid and efficient example (Scheme 1) features favourable tertiary carbenium ion generation by protonation of the alkene group in the precursor sulfonamide **1**, which is then trapped by the sulfonamide group to give an essentially quantitative yield of the corresponding pyrrolidines **2**.



Scheme 1. Intramolecular, acid-catalysed hydroamination.