STEREOSELECTIVE SYNTHESIS OF PYRROLIDINES BY INTRAMOLECULAR HALOAMIDATION

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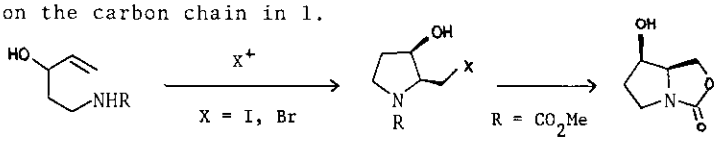
For the synthesis of biologically active natural alkaloid (e.g. Anisomycin, Retronecin), there is considerable interest in developing a general method for the stereocontrolled formation of pyrrolidine framework. We present a new and stereoselective synthetic method of N-substituted-cis-2-halomethyl-3-hydroxypyrrolidine 2 (Equation 1). The haloamidation of acetamide (R = COMe) or benzamide (R = COPh) was unsuccessful. As more acidic amides, we examined p-toluensulfonylamide (R = $SO_2C_6H_4$p-Me) and carbamate (R = CO_2Me). These amides nicely underwent the cyclization to give 2,3-cis-pyrrolidine derivatives. The halocarbamates (2, R = CO_2Me) were unstable and changed into bicyclocarbamates 3 partially during the haloamidation reaction at room temperature. this second cyclization was accelarated by explosing them to dipolar solvents (e.g. Acetonitrile). Compared with carbamates, sulfonylamides showed the higher reactivity and the higher selectivity as well as the higher flexibility of the substitution pattern on the carbon chain in 1.



1 2 3 1

As an extention of the above cyclization, we examined the haloamidation of 4-hydroxy-4-methyl-5-hexenylamid.This reaction proceeded to give piperidine derivatives not via an ionic but via a radical process.

The mechanistic aspects of the present reaction and its application to the natural product synthesis are under study.