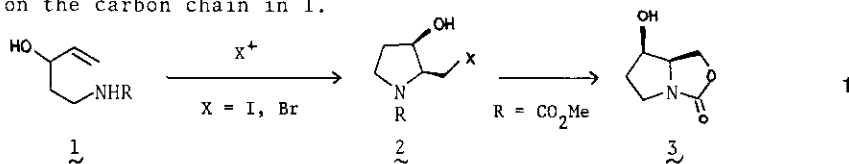


STEREOSELECTIVE SYNTHESIS OF PYRROLIDINES
BY INTRAMOLECULAR HALOAMIDATION

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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-hydroxy-pyrrolidine 2 (Equation 1). The haloamidation of acetamide (R = COMe) or benzamide (R = C₆H₅) was unsuccessful. As more acidic amides, we examined p-toluenesulfonylamide (R = SO₂C₆H₄p-Me) and carbamate (R = CO₂Me). These amides nicely underwent the cyclization to give 2,3-cis-pyrrolidine derivatives. The halo-carbamates (2, R = CO₂Me) were unstable and changed into bicyclocarbamates 3 partially during the haloamidation reaction at room temperature. this second cyclization was accelerated by exposing 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.



As an extension 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.