SYNTHESIS OF SPIRO-ISOXAZOLINES VIA INTRAMOLECULAR CYCLIZATION

Eric McClendon and Ashton T. Hamme II

Department of Chemistry, College of Science, Engineering and Technology, Jackson State University, 1400 Lynch Street, P.O. Box 17910, Jackson, Mississippi, USA

Abstract: Psammoplysins A-E are a family of natural products that were isolated from marine sponges of the order Verongida. Many of these natural products display antiviral and antineoplastic activities. The most interesting structural motifs of the psammoplysins are the oxipin and isoxazoline ring systems which are connected in a spirocyclic array. The synthesis of this type of ring system was accomplished in two steps. These synthetic processes involve a 1,3-dipolar cycloaddition and an intramolecular ring closure of a pendant alcohol onto an activated isoxazole. The 1,3-dipolar cycloaddition of an alkyne with α-chlorobenzaldoxime afforded the desired isoxazole. Intramolecular cyclization was achieved through the reaction of the isoxazole ring with bromine and sodium bromide in water. The proposed mechanism of intramolecular cyclization involves the activation of the isoxazoline ring with bromine to form a bromonium ion. Neighboring group participation of the oxygen can cause an opening of the bromonium ion intermediate and thereby give rise to an oxonium ion. Intramolecular attack of the alcohol oxygen onto the oxonium ring system and loss of a proton can then afford the spiro-isoxoline. The synthesis, mechanistic details, and isolated yields for the synthesis of our spiro-isoxoline compounds will be discussed.

Keywords: Spiro-isoxazolines, Cycloaddition, Regioselectivity, and Heterocycles.

Acknowledgments: This research was financially supported by: NIH-RCMI Grant Award Number G12RR13459-07S1.