SYNTHESIS OF SPIRO-ISOXAZOLINES VIA INTRAMOLECULAR CYCLIZATION

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Abstract: Psammaplysins 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 psammaplysins are the oxipin and isoxazoline ring systems which are connected in a spirocyclic array. This research will focus on synthesis of the isoxazole motif, which is highlighted above. The synthesis of this type of ring system is accomplished in two steps. These synthetic processes involve a 1,3-dipolar cycloaddition and an intramolecular ring closure of a pendant alcohol or carboxylic acid onto an activated isoxazole. The 1,3-dipolar cycloaddition of an alkyne with an α-chlorobenzaldoxime afforded the desired isoxazole. Intramolecular cyclization was achieved through the reaction of the isoxazole ring with an electrophilic source of bromine. 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 opening of the bromonium ion intermediate and thereby give rise to an oxonium ion. Intramolecular attack of the alcohol or carboxylic acid oxygen onto the oxonium ring system and loss of a proton should then afford the spiro-isoxazole. The intramolecular cyclization occurs in a very stereoselective manner whereby the bromine atom and the newly formed spiro-isoxazoline ring oxygen have an anti-relationship. The synthesis and mechanistic details for the synthesis of our spiro-isoxazoline compounds will be discussed.

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

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