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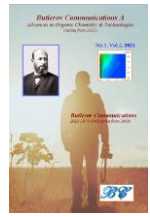

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Regioselectivity of 3-aryl-5-*N*-acylaminoisoxazoles sulfonyl chlorination

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Abstract

The great interest in sulfonylamide derivatives of heteroaromatic systems is due to their high and specific biological activity. They are widely used as inhibitors of human carboanhydrases involved in various biochemical processes. The main approach to the synthesis of sulfamide derivatives is the interaction of the corresponding sulfonyl chlorides with ammonia or amino compounds. An important step in the preparation of these compounds is the sulfonyl chlorination of the corresponding aromatic substrates. We have previously proposed a scheme for the synthesis of 3-aryl-5-*N*-acylaminoisoxazole sulfonyl derivatives. It has been found that, depending on the structure of the starting substrates, either hydrogen substitution products in the heterocycle or in the carboaromatic nucleus are formed regioselectively as a result of the monosulfonyl chlorination reaction. The presented article is devoted to the theoretical study of regioselectivity in sulfonyl chlorination reactions of 3-aryl-5-*N*-acylaminoisoxazoles using quantum-chemical modeling of the structure of substrates and resulting products by the method of density functional theory (DFT) in correlation-exchange hybrid potential (B3LYP) with the basis set 6-31G(*d,p*) in software FireFly 8.2. Calculations and comparative analysis of the energy characteristics of all possible isomeric sulfonyl chlorides made it possible to exclude thermodynamic control of the sulfonyl chlorination process of 3-aryl-5-*N*-acylamino-isoxazoles and conclude that the reaction is kinetically controlled. It has been found that the reaction center of the substrate is the carbon atom of the aromatic cycle, which makes the maximum contribution to the IBMO of the compound, that is, the direction of electrophilic attack is subject to orbital control. For 3-phenyl- and 3-(4-bromophenyl)-5-*N*-acylamino-isoxazoles, the hydrolysis of the amide bond initially proceeds under reaction conditions, and the subsequent sulfonyl chlorination of the resulting 3-aryl-5-aminoisoxazoles is subject to orbital control.

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