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ROZPRAWA DOKTORSKA

Badanie reakcji α,β-nienasyconych związków karbonylowych z reagentami binukleofilowymi

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An abstract from the PhD dissertation

The research undertaken in this dissertation was aimed at verifying the possibility of synthesis of 2-isoxazoline derivatives by the reaction of *α,β*-unsaturated aromatic-aliphatic ketones with hydroxylamine hydrochloride, as well as determining the probable mechanism of the reaction, including mainly the structure of the intermediate product, the site of attack of the nucleophile and its form.

In the studies conducted on the reactions of *α,β*-unsaturated ketones with hydroxylamine two groups of heterocyclic compounds was obtained: the 2-isoxazolines (yield 43 – 94 %) and 5-hydroxyisoxazolidines (yield 17 – 84 %). In both cases, a large molar excess of hydroxylamine hydrochloride and base was necessary.

A series of 5-hydroxyisoxazolidines has been successfully synthesized through tris(hydroxymethyl)aminomethane (TRIS) buffered hydroxylamine hydrochloride and *α,β*-unsaturated ketones reaction. The structure of 5-hydroxyisoxazolidines was confirmed not only by extended NMR analysis but series of elimination and acetylation reactions. Hydroisoxazolidines are obtained as a mixture of diastereomers (*cis*-, *trans*- and *N*-invertomers). Usually, three sets of ^{1}H NMR signals are observed for that class of compound (especially for protons H3 and both H4). Preliminary studies on the reaction mechanism indicated that *β*-carbon of *α,β*-unsaturated ketones, and the nitrogen atom of hydroxylamine are the active sites of reaction. Additionally, the synthesis of 4-isoxazoline from a two-step reaction of arylideneketone and hydroxylamine is reported (which has not been obtained so far by going directly from enones).

Synthesis of 3-aliphatic-5-aromatic(heteroaromatic)-2-isoxazoline was achieved by two different methods. First, by condensation arylideneketones with hydroxylamine hydrochloride upon treatment with excess sodium hydroxide. The second, by two-step reaction which involved the addition of hydroxylamine hydrochloride to arylideneketones (in the presence of pyridine) and then the acid-driven cyclization of obtained arylideneketone oximes. The second method has limited scope but the resulted 2-isoxazolines are obtained with a simpler purification procedure.

In addition to the exclusion of *α,β*-unsaturated oximes as intermediates, 3-hydroxyisoxazolidines, a pathway in which the nucleophilic center is an oxygen atom, were also excluded. Among other compounds, *β*-hydroxyamine oxime was found in the reaction mixture, which may be an intermediate product in the synthesis of 2-isoxazolidines. Regardless of the factor causing the elimination of the hydroxylamine molecule, the resulting *β*-oxime anion must undergo further transformations. The formation of *α,β*-unsaturated oxime can be expected, but this product was not observed under the conditions used. The resulting anion, due to its proximity to the aromatic system, may undergo resonance stabilization, in which the canonical form indirectly takes the form of *β,γ*-unsaturated oxime, and the *O*-anion of *β,γ*-unsaturated oxime has a much lower energy barrier needed for ring closure than the analogous *O*-anion of *α,β*-unsaturated oxime.