PP15. REGIOSPECIFIC SYNTHESIS OF 4,5-DIARYLISOXAZOLES BEARING CYTISINE MOIETY

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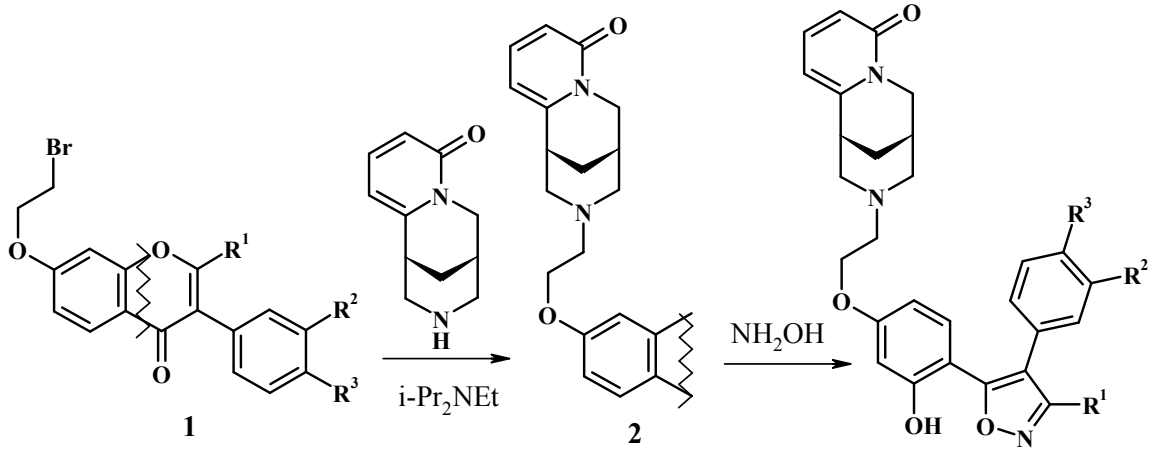
Isoflavonoids are known to be convenient intermediates for targeted synthesis of new N-containing heterocycles, the preparation of which by other methods is difficult or impossible.

Because 5-(2-hydroxyphenyl)-4-arylisoxazoles inhibit Hsp90, are anti-tubulins, and exhibit hypoglycemic activity, the development of synthetic methods for new derivatives of this series is extremely critical. N^{12}-(2-hydroxyethyl) derivatives of cytisine possess analgesic, antiarrhythmic, antihypertensive activity. The goal of this investigation is binding cytisine and 3,4-diarylisoxazole moieties in molecule, which can lead to new biological data results.

The simple synthesis of 3,4-diarylisoxazoles is re-cyclization of chromone derivatives under NH_2OH action. For the synthesis of target cytisine-isoxazole conjugates we studied interaction of hydroxylamine with 7-(2(cytisin-12-yl)ethoxy)isoflavones, which were synthesized by alkylation of cytisine with 7-(2-bromoethoxy)isoflavones in presense oh Hunig's base.



R^1 = H, Me; R^2, R^3 = H, OMe

Thus, reaction of hydroxylamine hydrochroride with compounds **2** (R^1 = Me) in pyridine led to formation only 2-methyl-3-aryl-4-(4-(2-(cytisin-12yl)ethoxy-2-hydroxyphenyl))isoxazoles **3**.

In case of 2-terminated isoflavones**2** the similar reaction led to formation of both regio-isomeric isoxazoles. It was found, the formation of target regio-isomeric isoxazoles**3** (R^1 = H) is possible in ethanol in presense of 4-methylmorpholine, which provide nucleophile attack in C-2 chromone ring.

The structures of 4,5-diarylisoxazoles **3**were confirmed by HSQC and HMBC spectra. In case of 2-methyl isoxazole derivatives with HMBC spectra were identified that 2-Me group is linked with carbon at 158-160 ppm, and carbon at 163-165 ppm is linked with phenolic substituent. The similar results were observed for compounds **3** (R^1 = H). It was identified with HSQC spectra, CH carbon shift was 151-152 ppm. These data are confirming regiospecific formation 4,5-diarylisoxazoles **3**.