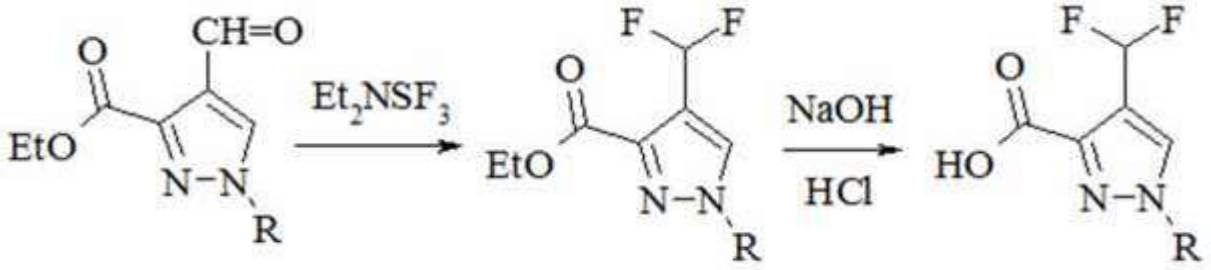
СЕКЦІЯ 5
АКТУАЛЬНІ ПИТАННЯ БІОЛОГІЧНОЇ ТА ФАРМАЦЕВТИЧНОЇ ХІМІЇ

Barus M. M.

A NEW APPROACH TO THE PREPARATION OF 4-DIFLUOROMETHYL-1*H*-PYRAZOLE-3-CARBOXYLIC ACIDS

Department of Medical and Pharmaceutical Chemistry
Bukovinian State Medical University

The introduction of fluorine atoms or fluoroalkyl groups in heterocyclic systems is fundamentally important for a significant increase in their biological activity. Due to its unique structure, the fluorine atom can give specific properties to various molecular scaffolds, in particular, significantly expand the weak binding interactions, increase metabolic stability, and even dramatically change the physicochemical behavior. In such processes, a special role belongs to the trifluoromethyl group, which has become a privileged structural element for the effective correction of pharmacokinetic parameters of heterocyclic structures. For example, among the biologically attractive functional pyrazoles, trifluoromethylated derivatives have become important for modern medical chemistry. Among them, the anti-inflammatory drug Celecoxib [4-{5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl} benzenesulfamide] deserves special attention, which belongs to the selective COX-2 inhibitors and is introduced into clinical practice for the treatment of osteo- and rheumatoid arthritis.



Difluoromethyl-containing pyrazoles are also compounds with a complex of biological action, although compared to trifluoromethyl analogues, they are studied to a much lesser extent. These include 3-aryl (heteroyl) substituted 4-difluoromethylpyrazoles, some of which contain cannabinoid receptor ligands, as well as substances that can be used to treat inflammatory diseases and diabetes. Not less important is their use in agrochemistry as a promising herbicide.

3-Carbofunctionalized 4-difluoromethylpyrazoles are studied to a much lesser extent and are presented in the literature only as an example of ethyl 1-methyl-4-di-fluoromethylpyrazole-3-carboxylate, although they appear to be quite convenient synthetic blocks for the design of various functional derivatives. Due to this, it seemed important to develop a preparatively convenient method for obtaining 4-difluoromethylpyrazole-3-carboxylic acids.

It is known that the interaction of the corresponding aldehydes with an effective fluorinating reagent diethylaminosulfur trifluoride (DEST) is usually used to modify organic compounds with a difluoromethyl moiety. Ethyl 4-formylpyrazole-3-carboxylates were selected as substrates for the difluoromethylation reaction. It was found that their interaction with a 2.2-fold excess of DEST in dichloromethane at room temperature leads to their formation with yields of 68-75%, 4-difluoromethylpyrazole-3-carboxylates in ^{1}H NMR spectra in the range of 9-10 m h. there are no singlets of CH-protons of the formal group and there are triplets of protons of the CHF_2 band in the range of 7.12-7.18 m h.

Treatment of the obtained esters with 10% sodium hydroxide solution at room temperature, and then further acidification of the reaction mixture with 20% hydrochloric acid allows to smoothly convert them to the corresponding acids, which were isolated with yields of 86-92%.