SYNTHESIS OF 4-AMINO-BENZO[*f*]ISOINDOLE DERIVATIVES BY REACTION 1-AMINO-2-ARYLISOINDOLES WITH MALEIMIDES

Derivatives of 4-amino-benzo[f]isoindole, also known as rearrangement products of the second type are object of interest from both practical and fundamental points of view. Thus, compounds containing succinimide fragment show diversified biological activity, including α-1A adrenergic receptor antagonist, androgen receptor antagonist, anxiolytic, antiviral, antibacterial, anti-inflammatory, antitumor, hypolipidaemic and fungicidal properties. Compounds with isoindole core should have antidepressant and anorexia effect. These compounds also have fluorescent properties. Methods of synthesis are interesting from the perspective of theoretical chemistry. The formation of these substances was first shown by our research group for example 2,4-dymetylpirimido[2,1-a]isoindole, where it was formed as a result of rearrangement of exo-adduct Michael-Diels-Alder reaction.

Another known method of synthesis is the interaction of bis-Michael adduct of acetylacetone in acetic acid saturated with hydrogen chloride.

This work is devoted to the study of the reactivity of substituted 1-aminoisoindoles in reactions with maleimides and synthesis of 4-amino-benzo[f]isoindole derivatives.

Previously, our research group has shown that in the reaction of 1-unsubstituted aminoisoindoles and its analogue 1-ethoxyisoindole with maleimids as a result of a number of successive transformations bis-Michael adducts are formed, because for the Curtine-Hammet principle it is needed only a small amount of initial reactants in equilibrium system for the successful completion of the reaction, and in case of 1-ethoxyisoindole depending on the substituent at the nitrogen atom in maleimide can be obtained mono- or bis-Michael adducts or there mixtures. In case of 1,2-dyarylisoindoles with fixed isoindole fragment interaction with maleimides follows the classical scheme and the rearrangement does not occur, but depending on reaction conditions Diels-Alder or Michael adducts are formed. Effect of substituents in the second position of 1-aminoisoindoles has not been yet studied. As you know, isoindole derivatives have a special type of tautomerism – isoindolo-isoindolenine tautomerism. In case of the second substituent in position 1 aminoisoindole loses the opportunity to be in isoindolenine tautomeric form, but the basic form remains isoindole and imine forms.

Starting 1-amino-2-arylisoindoles were synthesized from 2-methylbenzonitrile and the corresponding ortho-, meta- and para-aminophenols. It has been shown that reaction has good yields for ortho-and meta-substituted aminophenols, but in case of para-substituted aminophenol synthesis was ineffective because of formation of by-products, most likely oxidation products. Therefore, further work was carried on ortho- and meta-substituted aminophenols and corresponding isoindoles.

While studying the reaction in methanol at room temperature (conditions similar to the reaction of unsubstituted aminoisoindoles) in addition to the expected product was obtained also fluorescence product, the ratio of the reaction products was about 1:1. Reaction in isopropyl alcohol gave the same result. Since the initial isoindoles were as hydrobromide, the base form was generated in situ by addition of triethylamine. The formation of the reaction products can be imagined as successive attacks by Michael and Diels-Alder reaction followed by rearrangement in 7-azanorbornen system. There are two different rearrangement: 1)bond breaking in azanorbornen fragment is similar to such as in case of unsubstituted 1-aminoisoindoles 2) rearrangement, resulting in forming desired compound. In fact there are two parallel reactions.

By selecting of the reaction conditions was shown the possibility of kinetic control of the reaction. A number of conditions were investigated and selected the most promising to shift the equilibrium toward the formation of product. Compounds were obtained by the reaction at low temperature (~ 5°C) in acetonitrile. In this case, the main problem was the reaction speed (5–7 days) and relatively low yield (30%). It was also shown that a slight increase in temperature does not significantly change result of the reaction – at room temperature in acetonitrile reaction time remained within 5–7 days. Significant problem is the solubility of starting materials at low temperatures, resulting in significantly increased reaction time. The same can be explained for relatively low output, which may be slightly increased by the elongation of reaction time, however, this approach is not effective.

Therefore, it was tried to use relatively low-boiling solvents, thereby controlling the reaction temperature. Reaction in dichloromethane gave the opportunity to obtain pure product. This also significantly reduced reaction time to 4–5 hours.

Key words: isoindole, rearrangement, bis-Michael adduct.