Chemoselective reduction of amides to imines. Synthetic applications of the developed transformation.

The amide bond is one of the most important atom linkages known to science. Amide bonds link amino acids to each other to form proteins. The amide moiety is also widespread in pharmaceuticals and natural alkaloids. Due to its specific structure, this functional group is distinguished by remarkable stability and very low reactivity. People, inspired by nature, reach for amide derivatives willingly for the sake of making life easier or protecting it. Amides can be found in many products, starting from nylon for tights and ending with anaesthetics and antibiotics.

No wonder that this class of compounds is of interest to chemists around the world. For a long time it has been believed, though, that amides undergo any reactions only in harsh conditions and not many methods of using them in organic synthesis were known. The amide as a tool for obtaining other chemical compounds was used for the first time by Vilsmeier and Haack. In 1927, they have shown that formamide – the simplest of possible amides – can be used for obtaining another compound class – aldehydes. To do this one must transform the amide into a more reactive species – today we call such an action an activation.

One had to wait until the second half of the 20^{th} century for next examples of the usage of amide activation methodology, and research into this field started gaining momentum only with the beginning of the last decade. One of the most useful and selective methods of amide carbonyl group activation is their reduction by an organometallic zirconium complex called the Schwartz's reagent. This compound allows the transformation of the amide into an imine or an iminium salt and those easily undergo reactions with nucleophilic agents, which in general results in various amines. It has lately been proved that the reaction with Schwartz's reagent is highly chemoselective, which means that it can be carried out in the presence of other, even very sensitive, functional groups. As recently discovered, this can also be achieved with an iridium catalyst and an added reducing agent.

Due to the still untapped potential of the direct reduction of amides to imines, we decided to investigate this field in the course of this project. As the first task, we intend to work on a method of selective transformation of 1,2- and 1,3-dicarbonyl compounds to bifunctional compounds – amino acids, amino alcohols, and diamines – especially chiral ones, corresponding to those occurring in nature. These target compounds are of high value because of their widespread use in organocatalysis, coordination chemistry, and organic synthesis. We have already successfully conducted some preliminary experiments in this field, which confirms the feasibility of the envisioned approach.

As the other tasks, which can be realized simultaneously, we aim to use analogous methodology in the transformation of sugar-derived, readily available lactams to respective aminoazoles of potential biological and organocatalytic activity. Such a moiety can be utilized as a catalyst in fundamental organic reactions such as aldol, Mannich, Michael reaction, and many others. A considerable advantage in employing sugar derivatives as substrates would be the opportunity for facile fine-tuning of polar and lipophilic properties of the obtained products by manipulating the hydroxyl groups present in their structures. This is a crucial aspect of rational design of biologically active compounds and can also result in water-soluble organocatalysts invaluable in implementing the principles of green chemistry.

We believe that this research will be a great development of pioneering investigations conducted in the field of amide activation to date and it will result with the development of new synthetic methods attractive to professionals in the field of organic, medicinal, and materials chemistry.