A NOVEL MECHANOCHEMICAL METHOD FOR THE SYNTHESIS OF UNSYMMETRICAL DISULFIDES

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Organosulfur compounds, especially ones containing the S-S bonds, play an important role in many fields of studies, such as synthesis of nanomaterials, agriculture, polymer chemistry, inorganic and organic synthesis, and pharmaceutical chemistry. When it comes to medical applications, disulfides can be used indirectly, as drug carriers, or directly as active pharmaceutical ingredients. The sulfur-sulfur bond-bearing compounds are found to have great biocompatibility and to be easily cleaved by the disulfide reductase in the targeted area of the body, allowing for effective treatment. Recently, disulfides have begun to attract more attention when used as encapsulating agents. As directly acting active pharmaceutical ingredients, disulfides are applied for the treatment of various diseases and are mostly recognized for their antifungal and antimicrobial properties [1]. The mechanism of action of such compounds involves the deactivation of biochemical pathways by interacting with the active sites of the enzymes, rendering them unreactive in metabolic processes. For this reason, the most valuable disulfides are actually the unsymmetrical ones, containing the electrophilic center localized directly on one of the sulfur atoms. Such deployment of electrons facilitates the cleavage of the S-S bonds when subjected to the attack of nucleophile located in the active site of an enzyme. Up to this date, the synthesis of unsymmetrical disulfides, without the generation of symmetrical ones is troublesome. During our research, we found out that one of the solutions to this problem could be the application of mechanochemistry.

Mechanochemistry is a synthetic technique, which involves any process where the reaction is induced by the application of mechanical energy. The most renowned advantage of such methodology is the possibility of conducting the solid-state synthesis, omitting the usage of any solvents. From the purely synthetic perspective, mechanochemistry may also surpass conventional synthesis in other aspects like shortening the reaction time with a simultaneous increase in overall yield, alternating the pathways of the reaction, or lower energy consumption. Unfortunately, only a few available drugs have been synthesized using the mechanochemistry approach, so there is a huge need for the discovery of such synthetic procedures. In this work, we report the efficient synthesis of the unsymmetrical disulfides with the use of the mechanochemical ball-milling approach. During the research, we synthesized the alkyl-alkyl, alkyl-aryl, and aryl-aryl unsymmetrical molecules, without any sign of symmetrical products being generated. We were successful in the disposal of the solvent from the reaction mixture, as well as switching the base from triethylamine to more environmentally friendly sodium carbonate. These results could be a milestone in the modern synthesis of disulfides that find application in pharmacology.

[1] C. Jacob, Nat. Prod. Rep., 2006, 23, 851-863