Solid-state mechanochemical synthesis of thio-ureido acids

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Mechanochemical reactions by ball milling are highly efficient in the development of clean, atom-economical processes as they provide a greener means to conduct reaction as it avoids the use of bulk solvents, minimize the production of chemical waste, and access selectivity and reactivity that is difficult or even impossible to achieve under conventional solution-based conditions. As part of our research program in investigating the solid-state mechanochemical reactivity of amino-substituted reagents[1], we now report a simple, mechanochemical approach for the selective synthesis of thioureido acids, attractive for their role as catalysts in C-C bond-forming reactions, and antiglycating agents[2]. Although various synthetic approaches have already been developed for the synthesis of thioureido compounds, almost all these routes involve solution-based reactions requiring the use of stoichiometric base, bulk solvent and often requiring extended reaction times[3]. In contrast, the rapid mechanochemical direct coupling between unprotected zwitterionic amino-acids and thioisocyanates selectively forms the C-N bond and affords the desired thioureido products in a rapid fashion. On the other hand, performing a similar reaction in solution, using L-proline, can form an different bicyclic thiohydantoin product. Single-crystal X-ray diffraction crystallography was essential in the determination and characterization of the respective thioureido and bicyclic thiohydantoin products. This work further illustrates the outstanding potential of mechanochemistry to engage solid-state and structural chemistry as central to chemical synthesis.


Keywords: Mechanochemistry, Thioureido acids, C-N bond forming reactions