Development of Solid Base Catalysts for Hydroxypyrazine Synthesis in Water

(School of Science, The Univ. of Tokyo) ○Tomoya HISADA, Taku KITANOSONO,* Yasuhiro YAMASHITA, Shū KOBAYASHI*

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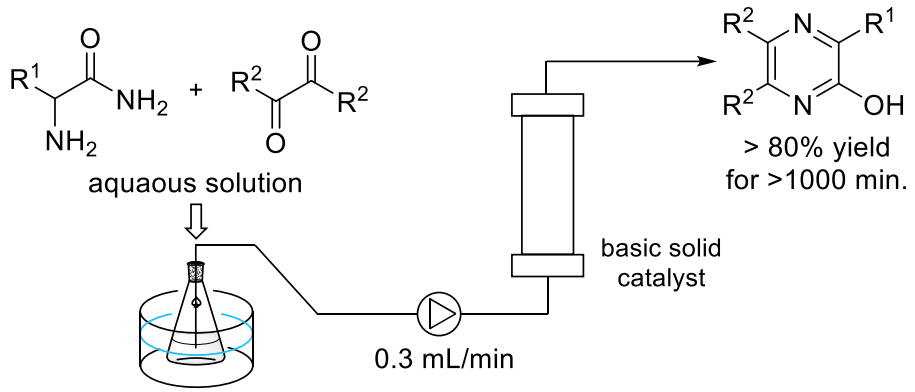
Hydroxypyrazine is an important structure in pharmaceuticals, and there is a need to establish an efficient method for the synthesis. Conventional synthetic methods require a large amount of phosphate buffer solution and an excessive amount of strong base, as well as a large amount of acid for quenching, which possess safety and waste problems.[1] The use of solid base catalysts can solve these problems, but there are few reports of solid base catalysts that can be used in water. On the other hand, our laboratory reported a heterocyclic formation reaction in water using a solid catalyst as environmentally friendly synthesis.[2] Here, we develop a solid base catalyst that can be used for hydroxypyrazine cyclization in water.

A-type zeolite and basic magnesium salts were found to catalyze the cyclization reaction of α-amino acid amides with glyoxal in water. This method can be applied to continuous-flow synthesis without use of any organic solvent. When a mixture of 2-aminomalonamide and glyoxal was pumped through a column packed with A-type zeolite, 3-hydroxypyrazinecarboxyamide, a precursor of favipiravir (an antiviral drug), was obtained in good yields.[3] Basic magnesium salts showed higher catalytic activity, catalyzing the cyclization reaction even at 5 mol% of loading under batch conditions. In addition, life time of basic magnesium salts was longer than that of A-type zeolites.



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