Green manufacturing: Short-step synthesis of fairy chemicals toward industrial production

○Arun Kumar Manna, Kohei Sato, Tetsuo Narumi, Kazuhiro Takeda, Nobuyuki Mase
(*Graduate School of Science and Technology, Shizuoka University*)
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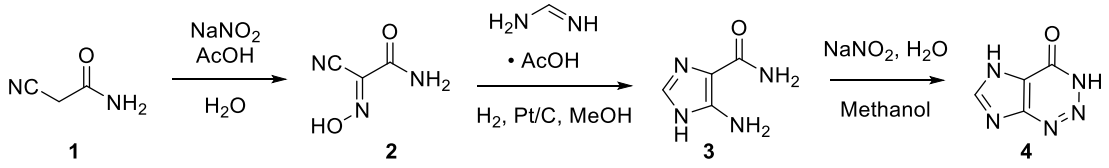
Fairy ring is commonly found in woodland, farmland, and agricultural land due to the fungus and plant interaction. Prof. Kawagishi *et al.* isolated AHX (2-azahypoxanthine), ICA (imidazole-4-carboxamide), and AOH (2-aza-8-oxo-hypoxanthine) from *Lepista Sordida* fungus and found a growth-regulating ability of these substances on bentgrass.[1] Recent interest in fairy chemicals (FCs) has been growing due to enhancing the adaptive nature of the plants against various environmental stress factors. As a result, the shoot, root elongation, and seed yield increased significantly.[2] 5-Amino-imidazole-4-carboxamide (**3**, AICA) is a crucial intermediate of fairy compound synthesis. AICA is prepared using high temperatures, long hours, and toxic reagents, which is a common synthetic method.[3] In this respect, we optimized the reaction condition in short-step synthesis and increased the yield percentage using modern fine-bubble organic synthesis and flow synthesis methods.[4]

Under batch conditions, approximately 81% of oxime **2** was obtained from cyanoacetamide (**1**) at room temperature using sodium nitrite and stirring overnight under acidic conditions. Then, we optimized the flow conditions and obtained 86% oxime **2** based on the yield optimum conditions (residence time: 15 min/74.0 °C). In the next step, a one-pot reductive coupling reaction was found to be more efficient than a two-step reaction. Next, we attempted to introduce our fine bubble method into the hydrogen reduction reaction. The multi-stacked elements-type fine bubble method showed more promising yields (60%, reflux, 6 h) than other conventional methods. Finally, AHX (**4**) was synthesized by the standard diazotization reaction and coupling reaction with AICA. The overall crude yield from oxime **2** to AHX was 30%.



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