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NOTE

An Improvement in Synthesis of 6-Ethyl-5-fluoro-pyrimidin-4-ol

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An effective and simple method for the preparation of 6-ethyl-5-fluoropyrimidin-4-ol is reported. It used formamide instead of formamidine acetate. It is new cyclization for synthesis of 6-ethyl-5-fluoropyrimidin-4-ol.

Key Words: Voriconazole, 6-Ethyl-5-fluoropyrimidin-4-ol, Formamide.

Voriconazole is a commercially marketed pharmaceutically active substance known to be useful for the treatment of some fungal infections. It exhibits excellent antifungal activity against a wide range of yeasts and filamentous fungi as demonstrated by *in vitro* and *in vivo* infection models with few observed side effects. Depending on the results of future clinical trials, this drug promises to become an important new agent in the treatment of invasive infections due to *Aspergillus* and other life threatening fungal infection[1,2]. 6-Ethyl-5-fluoropyrimidin-4-ol is the most important intermediate in the synthesis of voriconazole. There were two kinds of methods to prepare 6-ethyl-5-fluoropyrimidin-4-ol till now. The former method involves several steps, it had to use heavy metals catalysis and other costly material (Fig. 1)[3,4].

Whereas in the latter case, it had to using formamidine acetate, which is not cheap and obtained with difficulty (Fig. 2)[3,5-8]. However, these synthetic routes had been suffered from either high material cost or long steps. There are no efficient methods in reducing material cost and synthetic procedure for the preparation of 6-ethyl-5-fluoropyrimidin -4-ol and our interest in synthesis of voriconazole prompted us to search for a new, efficient, simple and low material cost methods.

The following reagents and solvents used in this preparation were sourced from some chemical company in China and used without further purification.

General procedure: Ammonia gas was passed with cooling (max 50 ºC.) through a solution of 88.9 g (0.6 mol) of methyl 2-fluoro-3-oxovalerate in 130 mL of formamide until no more NH_3 was taken up (about 1 h). The ammonia residues were removed by blowing out with nitrogen and applying a vacuum. The reaction solution was subsequently added dropwise to 450 mL of a 30 % NaOMe solution in methanol at 50 ºC. Addition of a further 50 mL of formarnide is followed by heating at 50 ºC for 3 h. The volatile constituents are evaporated under *vacuo* and subsequently the mixture was added to water and the pH is adjusted to 6 with HCl. Extraction with ethyl acetate and evaporation to provide 43.5 g of crude product, which was recrystallized from cold acetone. Yield: 34.8 g (40 %).

6-Ethyl-5-fluoropyrimidin-4-ol: m.p. 120-126 ºC. IR (cm^{-1}): 2986, 2883, 1687, 1659, 1611, 1240, 908. ^{1}H NMR: δ 1.26-1.29 (m, 3H), 2.70-2.76 (m, 2H), 8.03 (m, 1H). MS (ESI): 143 (M^+ + 1).

Detection method: Melting points were determined with a SGW X-4 micro melting point apparatus. IR spectra were determined as KBr pellets on a Bruker Vertex 70 spectrophotometer. ^{1}H NMR spectra were recorded using a Bruker-AMX 400 MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. ESIMS was recorded on Dionex MSOPlus mass spectrometer.

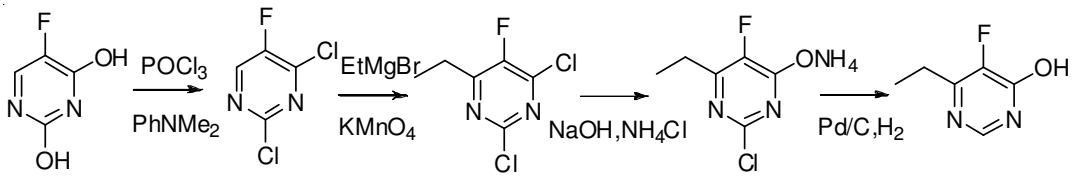

Fig. 1. First synthetic method of 6-ethyl-5-fluoropyrimidin-4-ol

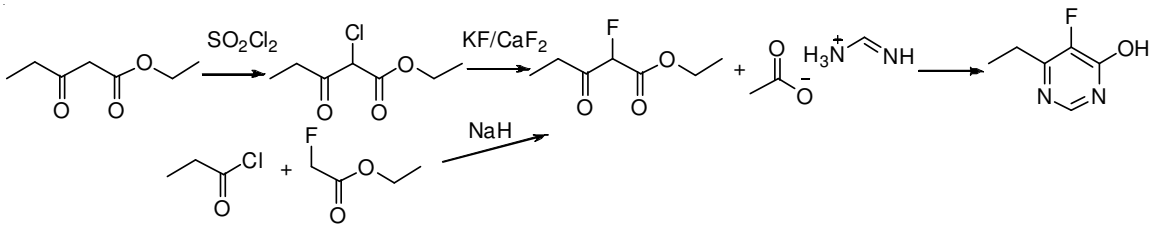

Fig. 2. Second synthetic method of 6-ethyl-5-fluoropyrimidin-4-ol

In connection with our research program directed toward the novel synthesis of 6-ethyl-5-fluoropyrimidin-4-ol, which was the important intermediate of voriconazole, here we reported synthesis of 6-ethyl-5-fluoropyrimidin-4-ol in a cheap and efficient way, from ethyl 2-fluoro-3-oxopentanoate, which could be easily prepared from ethyl 3-oxopentanoate or ethyl 3-oxopentanoate using formamide as cyclization regeants.

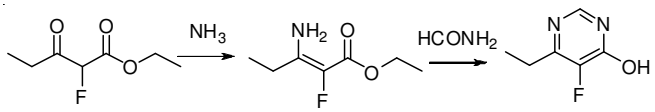

Fig. 3. New cyclization method.

First, we prepared 6-ethyl-5-fluoropyrimidin-4-ol by reaction of the ethyl 2-fluoro-3-oxopentanoate with ammonia, followed by treatment with formamide and sodium methoxide in methanol and obtained the product after purification (Fig. 3). The identities of compound was established by comparison of their physical and spectroscopic properties with those earlier reported[4].

Conclusion

In conclusion, an improved procedure of cyclization is reported by using the cheap starting materials which is easy to obtain. It is a rapid and convenient method to produce 6-ethyl-5-fluoropyrimidin-4-ol on a large scale at low cost. It is available for industrial production of voriconazole.

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