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An improved Synthesis of Ethyl 4-hydroxypyrimidine-5- carboxylate

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Starting from diethyl 2-(ethoxymethylene) malonate (EMME), the target molecule Ethyl 4-hydroxypyrimidine-5-carboxylate was synthesized at a yield of 90%. The one-step method for synthesis of the target molecule was simple with a higher yield of target product as compared to the reported methods.

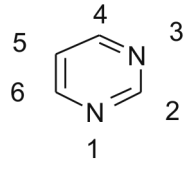
Key Words: Diethyl 2-(ethoxymethylene) malonate, Ethyl 4-hydroxypyrimidine-5-carboxylate.

Introduction

Virtually it seems that majority of commercially available pharmalogically active molecules are heterocycles and further N-heterocycles have attracted considerable attention of chemists as well biologists as a consequence of their exciting biological properties. Within nitrogen heterocycles, the synthesis, 1, 2 reactions, 3, 4 and biological activities 5, 6 of pyrimidine (1) containing molecules stand as an ever-expanding area of research in heterocyclic chemistry. Although compounds belonging to this group were known as break down compounds of uric acid at a very early date, the systematic study of the ring system really began with the work of Pinner7 who first applied the name pyrimidine to the un-substituted parent unit (1).

Pyrimidine or m-diazine is the parent ring system of a variety of substances which play a vital role in biological processes.8 this structural motif is also subset of a large number of pharmaceutical agents and naturally occurring substances such as vitamins, coenzymes, purines, nucleotides, and nucleic acids.

The properties of pyrimidines were governed to a large extent by the electron- attracting properties of the two nitrogen atoms; each reinforces the electronic effect the other in the 2-, 4-, and 6- positions. Therefore electrophilic attack will be generally retarded at these positions and nucleophilic attack is greatly facilitated. The 5-position is affected only by the inductive effect of the two nitrogen atoms there by making this position susceptible to electrophilic attack. The nucleophilic attack is difficult in this position compared to 2-, 4-, and 6- positions.



Pyrimidine
1

The pyrimidine nucleus had a wide occurrence in nature viz. in nucleic acids, nucleotides, in alkaloids obtained from tea, coffee, cocoa and in uric acid. Pyrimidine derivatives are very well known for their various therapeutic applications. Pyrimidine derivatives are used as anticancer9, anti-HIV10, antibacterial11, anti malerial12, antihypertensive13, sedetive hypotonics14, anticonvulsant15, antithyroid16, anti histaminic agents17, and anti biotics18. A recent review describes the significance of pyrimidine derivatives as anti-inflammatory agents19, and as vanilloid receptor antagonists20.

Most of the natural pyrimidines are hydroxyl and amino derivatives and a survey of the literature has revealed versatile application of Pyrimidine 5- carboxylates as anti bacterial, anti fungal, anticancer, H1-antihistamine, and anti-inflammatory agents. Based on these facts and in continuation of our research on heterocyclic compounds we synthesized Ethyl 4- hydroxy pyrimidine 5- carboxylate at ease without using any hazardous chemicals (Schme-1) with good yield when compared to the reported methods.

Materials and Methods

All the melting points were recorded on Fischer-Johns melting point apparatus and were uncorrected. Progress of the reaction and the purity of the compounds were tested

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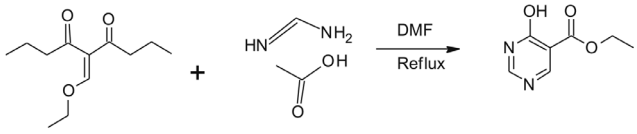
by using Thin Layer Chromatography (TLC) on silica gel. An IR spectrum was recorded using KBr pellets on Perkin-Elmer 683. 1H-NMR spectra was recorded on Varian Gemini 200 using TMS as standard, and CDCl3 as solvent and the chemical signals are represented as δ ppm. Mass spectra were recorded on a Micromass VG Autospec-M and Micromass Quattro LC-MS.

Experimental

Preparation of Ethyl 4-hydroxy pyrimidine 5-carboxylate:



2 **3** **4**

Scheme-1

To a stirred solution of Ethoxy methylene malonic ester (2.16gm/2ml, 0.01mol), in 10ml DMF, Formamidine acetate (1.25gm, 0.012mol) was added at room temperature. Then the reaction mixture was refluxed for 4 hrs and the red oily mixture was left overnight. Then 10 ml of water was added to the solid, and stirred it well for ½ hr. The solid was filtered, washed with cold water (2x10ml) and dried it well to get 1.5 gm of targeted compound with 90% yield with > 95% purity.

M.P: 1860C.

IR (KBr): 3350(-NH), 1720(>C=O), 1680(>C=O), 1570cm^{-1}(C=N).

1H NMR (CDCl3): δ 1.38 (t, 3H), 4.32 (q, 2H), 8.32 (s, 1H), 8.60 (s, 1H).

MS: m/z 168(M+).

Conclusion

The target molecule Ethyl 4-hydroxy pyrimidine 5-carboxylate was synthesized in one pot through a simple, nonhazardous and economically viable method. In this method we will get the target molecule with >95% purity with out doing any further purification or column chromatography.

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