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New Facile Method for Synthesis of 5-[(dimethyl amino) methylene] pyrimidine-2,4,6-trione as Potential Template for Barbiturate Drugs.

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ABSTRACT

New eco-friendly rapid Synthesis of 5-[(dimethyl amino) methylene] pyrimidine-2,4,6-trione was achieved by new method with efficient yield as potential template in synthesis of many biologically important organic compounds.

Keywords: Pyrimidine, Eco-friendly, New method, DMF-DMA, Barbituric acid

INTRODUCTION

Development of an efficient, and environmentally benign methods in organic synthesis is in great demand. In recent years many attractive strategies for synthesis of many lead compounds in a single step were achieved. Thereby, reducing the consumption of solvents, catalysts and energy, besides minimizing the generation of waste. In addition, the utilization of a catalyst having high recyclability feature promotes more environmental friendly benign protocol.

Although pyrimidine-2,4,6-trione (Barbituric acid) is pharmacologically inert, substitution at C-5 position imparts many pharmacologically important drugs1. Elbayaa et al2 find that substituted aminomethylenepyrimidine-2,4,6-triones scaffolds (I,II,III) are potential non-sedating, non-classic histaminergic (H1) blockers with low toxicity by incorporating aminomethylene side chain, Figure 1.

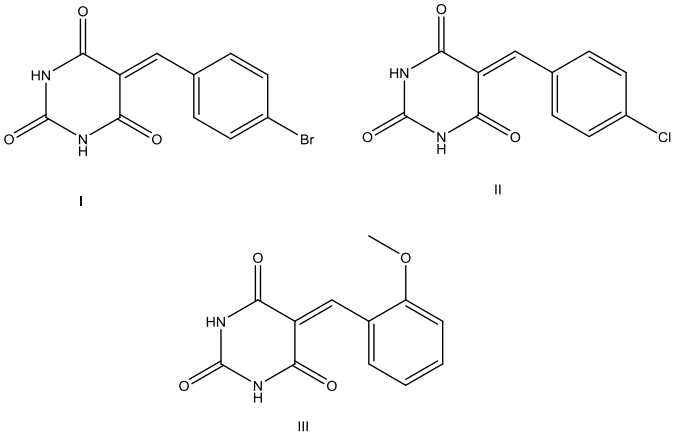

Figure 1: Non-sedating histaminergic (H1) blockers

Some of quinoline derivatives bearing 5-(amino methylene) pyrimidine-2,4,6-trione moiety showed excellent potency as c-Met kinase inhibitors3. Also, B. Stanovenik succeeded in synthesis of Aplysinopsin analogues (IV, V) as cytotoxic agents4 towards cancer cells starting from 5-dimethylaminomethylidene-2,4,6-pyrimidinetriones, Figure 2.

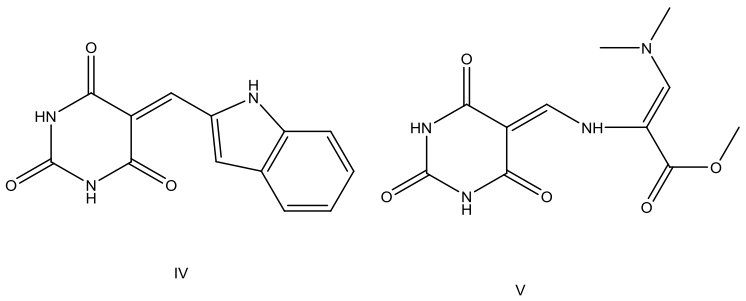

Figure 2: Aplysinopsin analogues as cytotoxic agents

These evidences prompt us to optimize fast, clean and an efficient method for preparing [(dimethylamine) methylene] pyrimidine-2,4,6-trione,because most of published methods used drastic conditions including more than one solvent in both reaction and purification beside energy and time waste reaching more than 48 hours for reaction to compete. Case in point; Yanfang Z. et al5 underwent aminomethylenation of pyrimidine-2,4,6trione using modified Vilsmier-Haak reagent N,N-dimethylformamidedimethylacetal(DMF-DMA) at 500C for 10 hours. On other hand this reaction were carried out by refluxing pyrimidine-2,4,6-trione in acetic anhydride/N,N-dimethylformamide for one hour 3at 90oC. Selic L. and Stanovnik B.4 suspended pyrimidine-2,4,6trione in dimethyl sulfoxide and stirred for 6 hours upon addition of (DMF-DMA).Fumio et al6 obtained mentioned aminomethylenation product via stirred pyrimidine-2, 4, 6 trione in dimethylformamide for 48 hours.

Amino-methylenation product also obtained via two step reaction using triethylorthoformate then reaction with substituted amine2.

MATERIALS AND METHODS

General information

Melting point were uncorrected and were taken in open capillaries on Stuart apparatus SMP30. Microanalyses were performed at the micro-analytical unit, Cairo University. Infrared spectra were determined in KBr on Brucker 5000FT-IR spectrometer (υ in cm.-1) .The 1H-NMR spectra were measured in CDCL3 using Jeol EX-500 MHz spectrometer. Mass spectra were recorded on GCMS-QP 1000 EX-Shimadzu gas chromatography US apparatus. Reaction times were determined using TLC technique on Silica gel plates 60 F245 E. Mark and the spots were visualized by U.V. (366nm) [1-6].

Chemistry

[(Dimethylamine) methylene] pyrimidine-2, 4, 6-trione. (VII)

To (12.8 gm, 0.1 mol.) barbituric acid, was added in dropwise manner (13.0 ml, 0.1 mol.), at room temperature (250C).The resulting yellow powder was triturated with petroleum ether (60/80),dried to yield amino methylation product in 98.5% yield. Anal.Calcd.For: C7H9N3O3 C,45.90;H,4.95;N,22.94 Found:C,45.87;H,4.82;N,22.91.m.p.2730C (decomposed). M/z (EI) 183.14(M+), ν max (KBr):3478, 3191, 1717, 1415. 1HNMR: 3.13 and 3.25 (3H, s N-(CH3)2, 8.16(1H, s, -CH=), 10.10 and 10.92 (1H, s,-NH)

RESULTS AND DISCUSSIONS

As a part of our research project aiming to the synthesis of novel non-sedating, H1 histaminergic blockers based on synthesis of new 5-substituted aminomethylenepyrimidine-2,4,6-triones as starting material that requiring reaction between pyrimidine-2,4,6-trione (VI) and DMF-DMA, we obtained a yellow fine crystals resulted at once upon drop wise addition of the reagent directly on pyrimidine-trione (VI) in open air system, which were triturated using petroleum ether (60/80) to give [(dimethylamine)methylene]pyrimidine-2,4,6-trione (VII) in 98.5% yield, Figure 3.

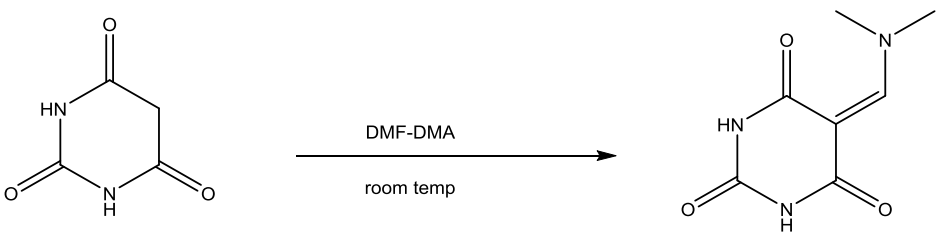

Figure 3: Amino methylene derivative.

CONCLUSION

We have discovered an unexpected direct amino methylenation of pyrimidine-2,4,6trione using modified Vilsmier-Haak reagent N,N-dimethylformamidedimethylacetal (DMF-DMA) at room temperature.

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