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An efficient and clean synthesis of *N*'-arylidene-6-hydroxy-2-methylpyrimidine-4-carbohydrazides

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ABSTRACT

6-Chloro-2-methylpyrimidin-4-ol ***(1)*** *reacts with carbon monoxide to give Ethyl-6-hydroxy-2-methylpyrimidine-4-carboxylate* ***(2)****. This ester is converted into hydrazide 6-Hydroxy-2-methylpyrimidine-4-carbohydrazide* ***(3)*** *and coupled with different aldehyde to obtain N'-Arylidene-6-hydroxy-2-methylpyrimidine-4-carbohydrazides* ***(4)****.*

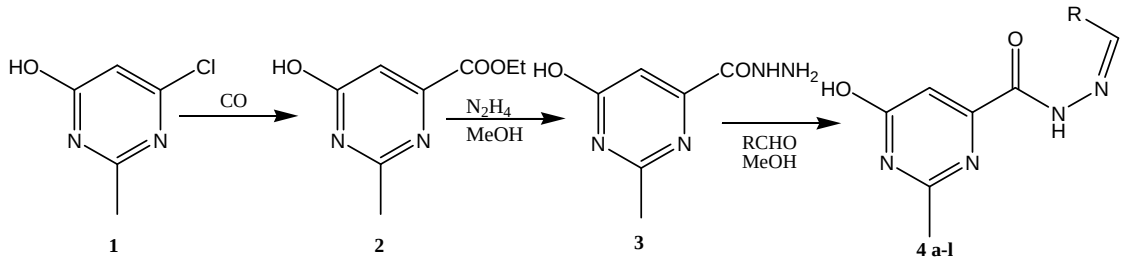
INTRODUCTION

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS. Alloxan is known for its diabetogenic action in a number of animals[1]. Uracil, thymine and cytosine are the three important constituents of nucleic acids.

The pyrimidine ring is found in vitamins like thiamine[2], riboflavin[2] and folic acid[2] Barbitone[1], the first barbiturate hypnotic sedative and anticonvulsant is a pyrimidine derivative[1]. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications such as anticancer agents[3,4] Antineoplastics[5], Drugs for hyperthyroidism[6], Antifolates[7], antibacterials[8] and antiprotozoals[9].

As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities[10].The synthesis of substituted pyrimidine and many detailed reviews have been appeared[12,13].

Scheme



MATERIALS AND METHODS

Experimental:
Chemicals and solvents were reagent grade and used without further purification. The ^{1}H NMR spectra were recorded in the indicated solvent on a Varian 500 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Brucher-IFS-66 FTIR spectrophotometer. The homogeneity of the compounds was checked using precoated TLC plates (E.Merk Kieselgel 60 F_{254}).

6-Hydroxy-2-methylpyrimidine-4-carbohydrazide (3):
Ethyl-6-hydroxy-2-methylpyrimidine-4-carboxylate (**2**) (0.02 mole) was dissolved in Methanol and hydrazine hydrate solution (98 % 0.02 mole) was added. The reaction mixture was heated at 65-70^{o}C for 3 hrs, under reflux. The solvent was removed under reduced pressure and the water was added until a yellow solid product is separated.

^{1}HNMR in DMSO-d_6: 2.38 (s, 3H), 4.51 (brs, 2H), 6.61 (s, 1H), 9.80 (brs, 1H), 12.65 (brs, 1H). Mass: m/z:169 (M+1).

***N*'-Arylidene-6-hydroxy-2-methylpyrimidine-4-carbohydrazide**
To a solution of 6-Hydroxy-2-methylpyrimidine-4-carbohydrazide (0.01 mole) in methanol (60 ml), aldehyde (0.01 mole) and a few drops of glacial acetic acid were added and the mixture was refluxed for 10 hours. It was then cooled, concentrated and poured into crushed ice and filtered. The solid thus obtained was purified by recrystallization from ethanol.

N'-Benzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
IR: 3343 cm^{-1} (NH), 3185 cm^{-1} (C-H aromatic), 1685 cm^{-1}(C=O), 1587 cm^{-1}(C=N); ^{1}HNMR in DMSO-d_6: 2.40 (s, 3H), 4.31 (q, 2H), 6.62 (s, 1H), 7.41-7.62 (m, 5H), 8.12 (s, 1H), 9.52 (brs, 1H), 12.65 (brs, 1H). Mass: m/z:257 (M+1).

N'-(4-Chlorobenzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.35 (s, 3H), 6.65 (s, 1H), 7.27 (d, 2H), 7.46 (d, 2H), 8.08 (s, 1H), 9.60 (brs, 1H), 12.65 (brs, 1H). Mass: m/z:292 (M+1).

N'-(2,6-Dichlorobenzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.38 (s, 3H), 6.66 (s, 1H), 7.38 (m, 3H), 8.12 (s, 1H), 9.28 (brs, 1H), 12.52 (brs, 1H). Mass: m/z:326 (M+1).

N'-(2-Chloro-4-(trifluoromethyl)benzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.41 (s, 3H), 6.62 (s, 1H), 7.40-7.55 (m, 3H), 8.15 (s, 1H), 9.18 (brs, 1H), 12.70 (brs, 1H). Mass: m/z:360 (M+1).

N'-(4-Fluorobenzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.35 (s, 3H), 6.65 (s, 1H), 7.32 (d, 2H), 7.56 (m, 2H), 8.07 (s, 1H), 9.55 (brs, 1H), 12.81 (brs, 1H). Mass: m/z:275 (M+1).

N'-(2-Fluorobenzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.35 (s, 3H), 6.68 (s, 1H), 7.35-7.58 (m, 4H), 8.08 (s, 1H), 9.52 (brs, 1H), 12.78 (brs, 1H). Mass: m/z:275 (M+1).

N'-(2,5-Dimethoxybenzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.38 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 6.61 (s, 1H), 7.85 (m, 3H), 8.15 (s, 1H), 9.51 (brs, 1H), 12.84 (brs, 1H). Mass: m/z:317 (M+1).

N'-(2,4-Dimethoxybenzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.35 (s, 3H), 3.76 (s, 3H), 6.65 (s, 1H), 7.84 (m, 4H), 8.12 (s, 1H), 9.48 (brs, 1H), 12.75 (brs, 1H). Mass: m/z:317 (M+1).

N'-(2-Cyanobenzylidene)-6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.37 (s, 3H), 6.68 (s, 1H), 7.44 (d, 2H), 7.78 (d, 2H), 8.10 (s, 1H), 9.52 (brs, 1H), 12.35 (brs, 1H). Mass: m/z:282 (M+1).

N'--(4-Phenylbenzylidene) -6-hydroxy-2-methylpyrimidine-4-carbohydrazide
^{1}HNMR in DMSO-d_6: 2.38 (s, 3H), 6.61 (s, 1H), 7.38 (d, 2H), 7.42-7.60 (m, 4H), 7.78 (m, 3), 8.10 (s, 1H), 9.38 (brs, 1H), 12.80 (brs, 1H). Mass: m/z: 333 (M+1).

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