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ECO-FRIENDLY SYNTHESIS OF *N*'-ARYLIDENE-6-HYDROXY-2-METHYLPYRIMIDINE-4-CARBOHYDRAZIDES

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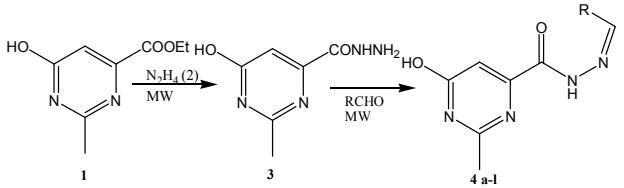
Abstract:
6-Chloro-2-methylpyrimidin-4-ol **(1)** reacts with carbon monoxide to give Ethyl-6-hydroxy-2-methylpyrimidine-4-carboxylate **(2)**. This ester is converted into hydrazide 6-Hydroxy-2-methylpyrimidine-4-carbohydrazide **(3)** and coupled with different aldehyde to obtain *N*'-Arylidene-6-hydroxy-2-methylpyrimidine-4-carbohydrazides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

Keywords: *Hydrazide, pyridimine derivatives, Arylidene, biological activity;*

Introduction:

The chemistry of nitrogen-sulfur heteroatom containing aromatic compounds is becoming more popular as an area of research. Phenothiazines and related compounds have shown diverse biological activities including as tranquilizers,[I] anti-inflammatory,[II] antimalarial,[III] antipsychotropic,[IV] antimicrobial,[V] antitubercular,[VI,VII] antitumour[VIII-X] and stimulation of the penetration of anticancer agents via the blood-brain barrier. They bind to physiological targets or receptors, producing many possible mechanisms of actions. However, solid cancers of the brain and stomach are generally resistant to chemotherapeutic agents.[XI]
Pyrimidine derivatives are of interest because of their pharmacological properties[XII-XXIII] including antiviral,[XXIV] antitumour,[XXV] antibacterial[XXVI-XXX] and antihypertensive[XXXI] effects. Several synthetic strategies have been reported for the preparation of pyrimidine derivatives. Most of these are based on modification of the classical one-pot Biginelli reaction and in some cases on more complex multi-step processes, which may involve the use of some expensive and commercially non-available materials. In view of the versatility of pyrimidines we here in report the synthesis of title compounds in an eco friendly process.

Scheme



Experimental:

Thin layer chromatography were run on silicagel-G and visualization were done using UV light or iodine. IR spectra were recorded by Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H –NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solvent using trimethylsilane as internal standard by 400MHz spectrometer. By Jeol-JMS D-300 spectrometer, mass spectra were recorded. Starting materials which were used in this chapter were obtained by commercial sources and used as such.

6-Hydroxy-2-methylpyrimidine-4-carbohydrazide (3):

Ethyl-6-hydroxy-2-methylpyrimidine-4-carboxylate (**1**) (0.02 mole) and hydrazine hydrate solution (98 % 0.02 mole) made as paste and irradiated under microwave 2-3 min. The crude was washed with water and 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) aldehyde (0.01 mole) and a few drops of glacial acetic acid were added and the mixture was irradiated under microwave for 2-3 min. 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).

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