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An Efficient and Convenient Synthesis of 4,6-Dichloro-2-methyl-5-nitropyrimidine

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A convenient synthesis of 4, 6-dihydro-2-methyl-pyrimidine can be obtained by cyclization reaction of acetamidine hydrochloride and diethyl malonate in the presence of sodium methoxide for a 91.2 % yield. 4, 6-Dihydro-2-methyl-5-nitropyrimidine can be achieved by nitration under the mixed acids of nitric acid, trichloroacetic acid and acetic acid in an 88.3 % yield and then the chlorination using phosphorus oxytrichloride can afford 4, 6-dichloro-2-methyl-5-nitropyrimidine with an 82.6 % yield.

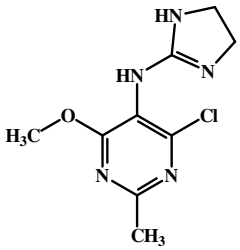
Keywords: Pyrimidine, Cyclization, Nitration, Chlorination, Synthesis.

INTRODUCTION

4,6-Dichloro-2-methyl-5-nitropyrimidine (**5**) was a key intermediate of the preparation of moxonidine (Fig. 1) (**1**), a new-generation centrally-acting antihypertensive drug to treat hypertension, which has been developed to control blood pressure effectively without the adverse effects of sedation and mental depression that usually are associated with centrally acting antihypertensive agents[1-4]. It had been reported that the preparation of moxonidine and its key intermediate 4,6-dichloro-2-methyl-5-nitropyrimidine[5,6]. Several syntheses of 4,6-dichloro-2-methyl-5-nitropyrimidine had also been reported in the literature[7,8]. Most of methods used are the hypertoxic trifluoroacetic acid, highly corrosive sulfuric acid and high-toxic N,N-dimethylaniline. A large quantity of waste water containing N,N-dimethylaniline was produced in the chlorination process for 4,6-dichloro-2-methyl-5-nitropyrimidine (**5**)[8-10]. It is very important for chemical scientist to use a clean and environmentally friendly technique. This paper reports an efficient and convenient synthesis of 4,6-dichloro-2-methyl-5-nitropyrimidine (**5**) utilizing a non-toxic acetic acid, low-toxic trichloroacetic acid and environment friendly chlorination reaction using triethylamine catalyst in good yield.

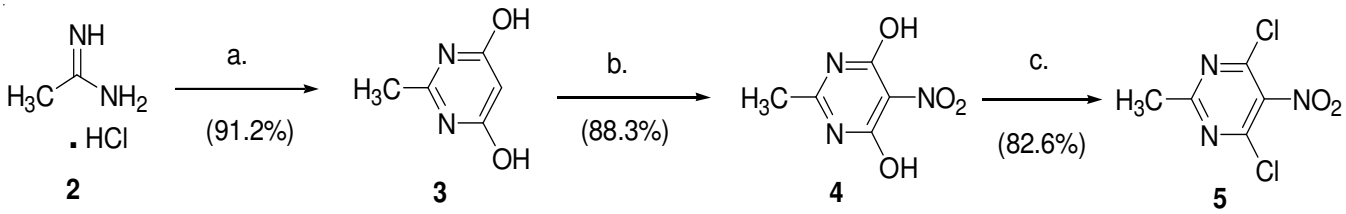
EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers and were used without further purification. All melting points were determined on a XT34 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. ^{1}H NMR spectra were recorded on Mercuryplus 400 (300 MHz) spectrometer, chemical shifts (δ) were reported in parts per million relative to tetramethylsilane. Chemical shifts were reported in parts per million relative to the solvent resonance as the internal standard ($CDCl_3$, δ = 7.16 ppm). Analytical TLC and column chromatography were performed on silica gel GF254 and silica gel H60, respectively.



Moxonidine 1

4,6-Dihydroxy-2-methylpyrimidine (2): 30 % Sodium methoxide solution in methanol (275.5 g, 1.53 mol) was added slowly to a mixture of acetamidine hydrochloride **2** (47.3 g, 0.50 mol), diethyl malonate (76.5 g, 0.52 mol) and methanol (200 mL) at room temperature. The mixture was stirred and heated under reflux for 3 h. The reaction mixture was cooled to room temperature. The resulting solid was collected by filtration, washed with methanol and then dissolved in 350 mL water. The aqueous solution was acidified to pH 2 by addition of concentrated hydrochloric acid under ice-cooling. The formed precipitate was separated by filtration, washed with water and methanol to give 57.5 g (91.2 % in yield) 4,6-dihydroxy-2-methylpyrimidine (**3**) as a white crystalline solid, m.p. 338-345 °C, (lit[8] m.p. 260-350 °C). ^{1}H NMR: (400 Hz, DMSO-d_6), δ (ppm): 11.76 (s, 2H, -OH), 4.97 (s, 1H, CH-), 2.20 (s, 3H, CH_3-).



a. diethyl malonate, CH_3ONa/CH_3OH b.HNO_3, trichloroacetic acid, acetic acid C. $POCl_3$, $(C_2H_5)_3NH$

Scheme-I:

4,6-Dihydroxy-2-methyl-5-nitropyrimidine (4): Nitric acid (7 mL, 0.15 mol, 90 % aqueous solution) was added slowly to a mixture of trichloroacetic acid (8.2 g, 0.05 mol), acetic acid (85 mL, 1.50 mol) and 4,6-dihydroxy-2-methylpyrimidine (**3**) (12.6 g, 0.10 mol) in an ice bath below 5 °C. Stirring was continued for 5 h at 15-20 °C, cooled below 5 °C and diluted with 200 mL of ice water. The resulting precipitate was collected by filtration and washed with water. recrystallization from water followed by drying in the vacuum oven provided 15.1 g (88.3 % in yield) 2-methyl-4,6-dihydroxy-5-nitropyrimidine (**4**) as a white crystalline solid. m.p. 286.6-287.8 °C (decomp.) (Lit[11] m.p. 287-288 °C (decomp)). ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 3.93 (s, 3H, CH_3-). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 161.7, 155.7, 117.8, 17.9.

4,6-Dichloro-2-methyl-5-nitropyrimidine (5): Triethylaniline (16.8 mL, 0.12 mol) was added slowly to a mixture of 4,6-dihydroxy-2-methyl-5-nitropyrimidine (**4**) (17.1 g, 0.10 mol) and phosphoryl chloride (46.5 mL, 0.50 mol) below 75 °C. The mixture was stirred and heated under reflux for 4 h. Excess phosphorus oxychloride was removed by distillation *in vacuo* and the residue was poured onto ice water (150 mL) and then extracted with ethyl acetate. The organic layer was washed with water and then with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. Thereafter, the solvent was distilled off *in vacuo* and the resulting crude product was recrystallized with petroleum ether (90-120 °C) and obtained 17.2 g (82.6 % in yield) 4,6-dichloro-2-methyl-5-nitropyrimidine (**5**) as a yellow crystal. m.p. 53.1-54.7 °C (Lit[8] m.p. 53-54 °C). ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 2.58 (s, 3H, CH_3-). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 27.1, 126.6, 153.8, 170.7.

RESULTS AND DISCUSSION

Recently studies using the imidazoline receptor agonists' moxonidine and a key intermediate 4,6-dichloro-2-methyl-5-nitropyrimidine, showed that the efficient synthesis of 4,6-dihydro-2-methyl-5-nitropyrimidin with chlorination in the presence of triethylamine catalyst can produce 6-dichloro-2-methyl-5-nitropyrimidine in very high yields. Meantime, the optimization of the synthetic conditions for 4,6-dihydroxy-2-methyl-5-nitropyrimidine and 4,6-dihydroxy-2-methylpyrimidine were conducted.

Preparation of 4,6-dihydroxy-2-methylpyrimidine is the cyclization of diethyl malonate and acetamidine hydrochloride under an alkali metal alkoxide such as sodium methoxide, sodium ethoxide. Sodium metal is inconvenient to use and is danger to prepare the solution of sodium methoxide or sodium ethoxide in lab. 30 % sodium methoxide-methanol solution is very common and cheap raw materials in China's chemical industry and it was found that 30 % sodium methoxide-methanol solution can obtain the good yield of 4,6-dihydroxy-2-methyl-5-nitropyrimidine. The yield of cyclization was 91.2 %.

Trifluoroacetic acid is a hyper-toxic reagent, which has limited use in the world. Sulfuric acid is highly corrosive acid. Generally, the non-toxic or environment friendly reagents for manufacture should be used. Although acetic acid is lower than trifluoroacetic acid in the performance of acid, it is non-toxic acid. Acetic acid was selected as a mixed acid medium for nitration and it was found that trichloroacetic acid can improve the yield of the 4,6-dihydroxy-2-methyl-5-nitropyrimidine. The yield of nitration was 88.3 %.

The traditional chloride reaction process usually adopts N,N-dimethylaniline as acid binding agent catalyst which produces the serious pollution of N,N-dimethylaniline, which is high-toxic reagent with carcinogenic, neurotoxic and blood poisoning. The acid binding agent catalyst in chlorination technique is needed some environment friendly reagents. The 4,6-dihydroxy-2-methyl-5-nitropyrimidine was treated with chlorination reduction using phosphorus oxytrichloride in the present of triethylamine catalyst to give 4,6-dichloro-2-methyl-5-nitropyrimidine in 82.6 % yields (**Scheme-I**).

Conclusion

Present contribution describes the use of triethylamine catalyst as a non-toxic reagent for the chlorination of 4,6-dihydroxy-2-methyl-5-nitropyrimidine. A convenient process for the synthesis of 4,6-dichloro-2-methyl-5-nitropyrimidine has been proven to be practical. The current method presents a promising synthetic process for 4,6-dichloro-2-methyl-5-nitropyrimidine because of the following advantages: (1) Simplicity of process in cyclization, because it is easy to get 30 % sodium methoxide-methanol solution in oxidation, (2) Simplicity of product purification, (3) The process is environment friendly with high yield, (4) Also the protocol reported in this paper can be easily developed into large-scale preparation of 4,6-dichloro-2-methyl-5-nitropyrimidine for new antihypertensive medicines development.

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