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Process chemistry of 4, 6-dihydroxy-2-methylpyrimidine-A potential precursor in pharmaceutical and explosive industries

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ABSTRACT

4,6-Dihydroxy-2-methylpyrimidine as an important precursor, find widespread applications in the preparation of high explosives and medicinal valued products. The synthesis of 4,6-dihydroxy-2-methylpyrimidine has been carried out by the condensation of acetamidinium chloride and diethyl malonate in absolute methanol and further acidified by hydrochloric acid. Process chemistry has been studied by using various alcohols, alkoxides and effect of reaction period. The role of process variables and parameters has been understood thoroughly and developed an economic process. Modified process yielded the product without compromising on its quality, which was confirmed by spectroscopic techniques and elemental analysis. Hence, the study finds its usefulness in the development of an economic process for the production of 4, 6-dihydroxy-2-methylpyrimidine.

KEYWORDS

4, 6-Dihydroxy-2-methylpyrimidine;
FOX-7;
Process chemistry;
Optimisation.

1. INTRODUCTION

4, 6-Dihydroxy-2-methylpyrimidine a potential molecule, find applications in pharmaceutical and explosive industries. This molecule and its derivatives have proved to be active candidates in the treatment of inflammation, hypertension, anxiety etc. The derivatives of this molecule have potent effects of inhibiting ACAT activity and lowering serum cholesterol[1,2] and also extremely useful for the treatment and/or prevention of arteriosclerosis or hyperlipidemia[3]. The substituted pyrimidine-4, 6-diones are often being used in many organic reactions[4]. 4, 6-Dihydroxy-2-methylpyrimidine is also an important precursor for the preparation of an insensitive high explosive 1, 1-diamino-2,2-dinitroethyl ene (FOX-7)[5,6]. Although several routes have been reported for preparation of FOX-7[7] but promising and versatile route is nitration of 4, 6-dihydroxy – 2 – methylpyrimidine[8,9]. Present manufacturing process of 4, 6-dihydroxy-2-methylpyrimidine involves condensation of acetamidinium chloride and diethyl malonate in the presence of organic alkali[10]. The process utilizes absolute ethanol for the preparation of sodium ethoxide. Thus, ethanol acts as reaction medium and it makes the process expensive. Longer process time and temperature is also contributed for the higher cost. As the molecule finds vital applications in pharmaceutical and explosive industries, it is necessary to develop an economic process for the manufacture of 4, 6-dihydroxy-2-methylpyrimidine without losing the quality of the product by studying the process chemistry of reaction. Hence, the present investigation focused on the process chemistry of 4, 6-dihydroxy-2-methylpyrimidine and studied the effect of process parameters like solvent, reagents,

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TABLE 1: Role of solvent on the product yield

Sr. no.	Solvent	Alkali	Reagent	Reflux time (h)	Reflux temp. (^{0}C)	Yield (%)
1	Ethanol	EtONa[a]	DEM	5	78	79
2	Ethanol	EtONa[a]	DEM	3	78	83
3	Methanol	MeONa[a]	DEM	5	64	81
4	Methanol	MeONa[a]	DEM	3	64	85

a - Freshly prepared from sodium and alcohol

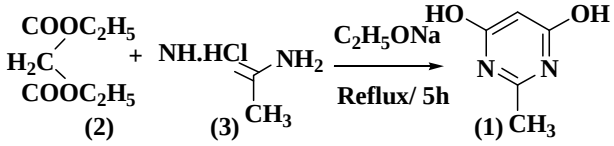

Figure 1 : Reaction scheme

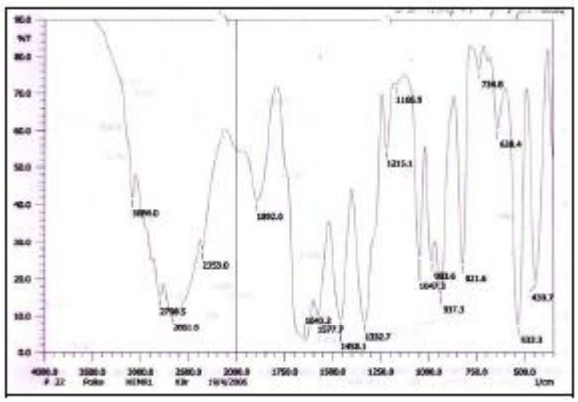

Figure 2 : FT-IR spectrum

time etc. to establish the economic process.

2. EXPERIMENTAL

General method of preparation of 4, 6-dihydroxy-2-methylpyrimidine

(i) Preparation of sodium methoxide

25.5 g of sodium is reacted with 400 mL dry methanol at 20^{0}C in a 1L jacketed glass reactor having lid and reflux condenser.

(ii) Reaction of acetamidinium chloride and diethyl malonate

The above prepared sodium methoxide solution was added with 50g acetamidinium chloride and 81mL diethyl malonate at room temperature. This mixture was stirred to 3 hours under reflux condition and then cooled to room temperature. The solid was filtered and washed with methanol and dissolved in water. The aqueous solution was acidified to pH 2 with concentrated hydrochloric acid at about 10^{0}C. The precipitate was filtered, washed with water and dried.

Similarly, the experiments were carried out by varying process parameters. Methanol was replaced with absolute ethanol and diethyl malonate by dimethyl malonate in stoichiometric proportions in different set of experiments. The reaction was also carried out to evaluate the role of different organic alkalies and their forms on the product yield like sodium ethoxide and methoxide powder and solution and potassium butoxide. The strength of alkali during the reaction course was monitored titrimetry. In a set of experiments, by varying the reflux time from 0.5 to 6 hours, optimized the reaction time.

The obtained product has been characterized by spectroscopic techniques, thermal and elemental analysis etc. The IR spectra were recorded on PerkinElmer FTIR-1600 spectrophotometer in KBr matrix and ^{1}H NMR spectra scanned on a 300 MHz Varian instrument in deuterated dimethyl sulfoxide at 30^{0}C with TMS as an internal standard. The DSC studies were undertaken on a PerkinElmer DSC-7 instrument at the heating rate of 10^{0}C/min in nitrogen atmosphere.

3. RESULTS AND DISCUSSION

Process chemistry plays an important role in developing an appropriate and economical process. Understanding the role of process parameters on the product yield will facilitate in evolving with an absolute process[11]. Figure 1 show, the basic route for synthesis of 4, 6-dihydroxy-2-methylpyrimidine from condensation reaction of acetamidinium chloride and diethyl malonate in the presence of sodium ethoxide[6,10].

For the same reaction scheme, process parameters have been varied systematically to realize role of each parameter on the yield of 4, 6-dihydroxy-2-methyl pyrimidine. TABLE 1 shows details of experiments and the obtained yield.

The synthesized 4, 6-dihydroxy-2-methylpyrimidine was characterized by spectroscopic tools. FT-IR spectrum of 4, 6-dihydroxy-2-methylpyrimidine is shown in figure 2. The absorptions at 3084, 1680, 1639, 1577, 1460, 1336, 532, 441 cm^{-1} confirms the functional groups. ^{1}H NMR spectrum was recorded in DMSO - d_6 (Figure 3) and the peaks at δ 2.215 (s, 3H); 4.950 (s, 1H); 11.674 (s, 2H) confirmed the presence of me-

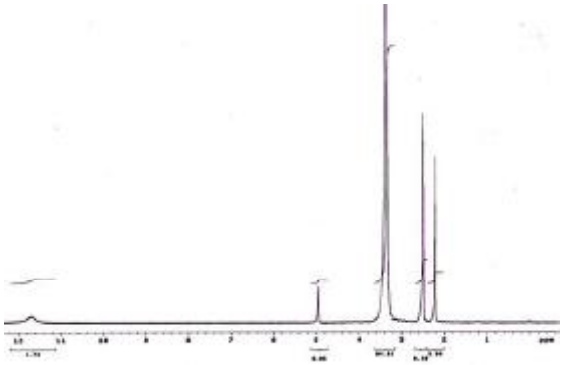

Figure 3 : ^{1}H NMR spectrum

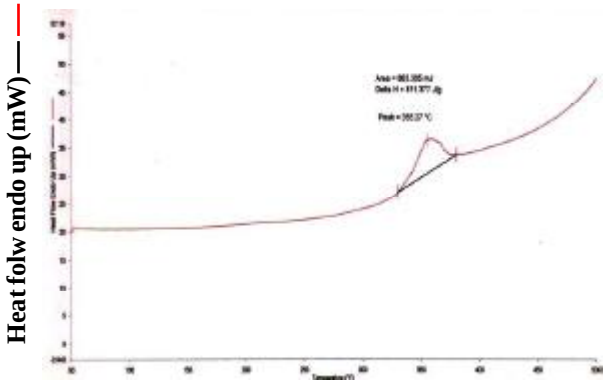

Figure 4 : Differential scanning calorimetric profile

TABLE 2 : Influence of nature of alkali on the yield

Sr. no.	Solvent	Alkali	Reagent	Reflux time (h)	Yield (%)
1	Ethanol	EtONa[a]	DEM	3	83
2	Ethanol	EtONa[b]	DEM	3	71
3	Methanol	EtONa[d]	DEM	3	67
4	Methanol	MeONa[a]	DEM	3	85
5	Methanol	MeONa[c]	DEM	3	80
6	Methanol	MeONa[d]	DEM	3	66
7	Methanol	t- BuOK[d]	DEM	3	57

[a]Freshly prepared from sodium and alcohol; [b]Solution of 20% EtONa in ethanol; [c]Solution of 30% MeONa in methanol; [d]Dry powder of alkoxide

thylene, methyl and hydroxy protons respectively of 4, 6-dihydroxy-2-methylpyrimidine. Endothermic peak at 355^{0}C in differential scanning calorimetric study confirms the melting behavior of 4, 6-dihydroxy-2-methylpyrimidine (Figure 4). The stoichiometric formula of the compound was ascertained by the elemental analysis. The estimated values found to match with the calculated carbon, hydrogen, and nitrogen contents.

3.1 Role of solvent

Nature and purity of the solvent alters the reaction rate and cost of the solvent also contributes significantly for the process cost. The use of a polar solvent will greatly increase the rate of ionization of substrate in nucleophilic substitution reactions. A rough indication of a solvent's polarity is a quantity called the dielectric constant. The dielectric constant is a measure of the solvent's ability to insulate opposite charges from each other. Electrostatic attractions and repulsions between ions are smaller in solvents with higher dielectric constants. Water is the most effective solvent for promoting ionization, but most organic compounds do not dissolve appreciably in water. They usually dissolve, however in alcohols, and quite often mixed solvents are used. The reaction between acetamidinium chloride and diethyl malonate is basically nucleophilic substitution at the acyl carbon. Hence, the polar methanol (dielectric constant = 33) was used instead of absolute ethanol (dielectric constant = 24) as a reaction solvent[12]. TABLE 1 reveals that changing the solvent from ethanol to methanol not only increases yield but also minimizes the reaction time. Further, this condensation reaction is effected by refluxing the solvent. Utilization of methanol brings down reflux temperature to 64^{0}C, which saves the power consumption to raise the temp to 78^{0}C in the case of ethanol as a solvent.

3.2 Influence of nature and strength of alkali on yield

The presence of strong alkali facilitates the formation of barbituric acid from diethyl malonate and urea[12]. As 4, 6-dihydroxy2-methyl pyrimidine is a structural analogous of barbituric acid, the reaction of aceta midinium chloride and diethyl malonate is also similar to the formation of barbiturates. Sodium and potassium alkoxides are often used as bases in organic synthesis due to their solubility in alcohol solvent rather than in water. In order to realize the effect of alkali on the reaction yield, different alkalies like ethoxide and methoxide of sodium and tertiary butoxide of potassium were attempted.

The effect of the alkalies on the yield are capitulated in TABLE 2 and it reveals the freshly prepared sodium methoxide by the reaction of sodium and methanol yields maximum amount of product of about 85% in contrast to 83% from freshly prepared sodium ethoxide. Freshly prepared sodium methoxide, gave better yield than its 30 % stock solution (E-Merck, LR). This may be due to loss of virginity of alkali strength of

available solution (trade). Similarly poor yield is observed by the direct use of sodium methoxide and ethoxide powders dissolved in methanol and ethanol, respectively. Better yield by using freshly prepared sodium methoxide compared to sodium ethoxide and potassium t-butoxide may be due to the better stabilization of reaction intermediate formed during for the formation of 4, 6 dihydroxy 2-methyl pyrimidine. The pK_a values of methanol (pK_a=15.5), water (pK_a =15.74) and ethanol (pK_a=15.9) are closer and their conjugate alkalis are also equally powerful in contrast to t-butanol (pK_a=18). This reveals that the condensation reaction requires moderately powerful alkali. Hence, more the alkali strength poor are the yield. Further, the use of sodium methoxide reduces the overall cost of the process since the process uses relatively cheap dry methanol as compared to absolute ethanol and better yield. The change of basicity during addition of reagents and reaction has been recorded (Figure 5), which may be due to formation of alcohols, and further stabilization of intermediate in the form of sodium salt.

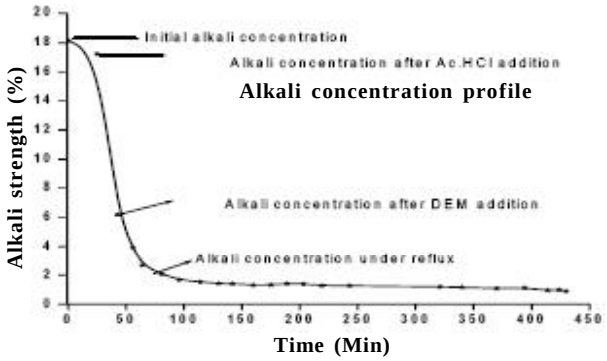

Figure 5 : Alkali strength monitoring during course of reaction

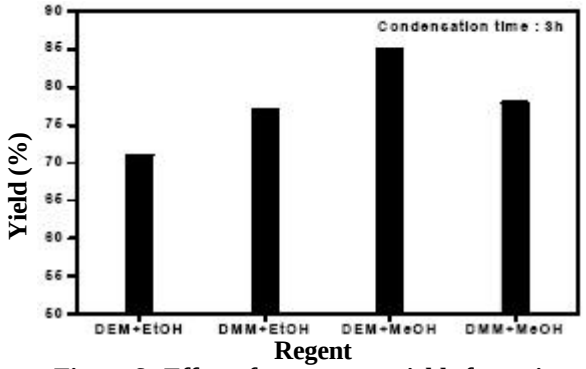

Figure 6 : Effect of reagents on yield of reaction

3.3 Influence of reagent on the yield

Reaction between acetamidinium chloride and diethyl malonate can be characterized as nucleophilic substitution reaction as mentioned earlier. The initial step in this type of reaction is nucleophilic addition at the carbonyl carbon atom. The initial attack is facilitated by following factors: the relative steric openness of the carbonyl carbon atom and the ability of the carbonyl oxygen atom to accommodate an electron pair of the carbon-oxygen double bond. The intermediate formed from an acyl compound usually eliminates a leaving group; this elimination leads to regeneration of the carbon-oxygen double bond and to a substitution product. The overall process in this acyl substitution follows nucleophilic addition-elimination mechanism. The reactivity of acid derivatives can be explained by taking into account the basicity of the leaving groups. Acyl compounds react as they do because they all have good leaving groups attached to the carbonyl carbon atom. Esters generally undergo nucleophilic substitution by losing a molecule of an alcohol, which is a weak alkali and is reasonably good leaving group. In the present investigation esters like diethyl malonate (DEM) and dimethyl malonate (DMM) in ethanol and methanol solvents were attempted. The reaction involves the elimination of weak alkalies of ethanol and methanol by the use of DEM and DMM, respectively. Figure 6 reveals that the DEM in methanol results overall better yield. No significant change in yield is observed while usage of DMM in methanol and ethanol. Further, cost of DMM makes it as ineligible candidate for the economic production of 4, 6 dihydroxy 2-methyl pyrimidine.

3.4 Optimization of reaction time

Process optimization is aimed to design a chemical plant at lowest total costs, while satisfying the quality of product and market requirements. Chemical processes are highly non-linear systems with optimum settings existing for most of the independent variables in the system. The reactor is usually the most important entity of equipment for which selecting best values for the independent variables, because its operations has a direct effect on raw material costs, and the composition of the reactor outlet stream determines the cost of the product work-up section of the plant[11]. Optimization of reaction time plays a vital role in significantly reducing cost. Minimized reaction time not only reduces utility costs but also improves the product yield and maximizes the overall productivity of the process.

TABLE 3: Optimization of reaction time

Sr. no.	Solvent	Alkali	Reagent	Reflux time (h)	Yield (%)
1	Methanol	MeONa[a]	DEM	0.5	79
2	Methanol	MeONa[a]	DEM	1	78
3	Methanol	MeONa[a]	DEM	2	80
4	Methanol	MeONa[a]	DEM	3	85
5	Methanol	MeONa[a]	DEM	4	81
6	Methanol	MeONa[a]	DEM	5	81
7	Methanol	MeONa[a]	DEM	6	81

[a]Freshly prepared from sodium and alcohol

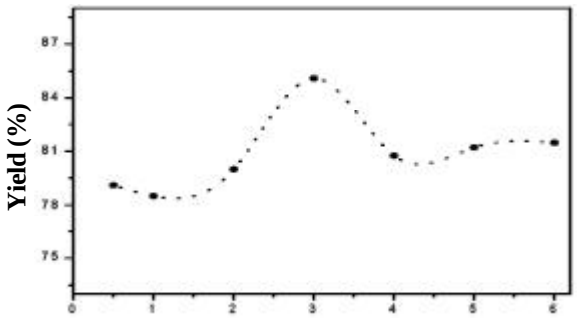

Figure 7: Effect of reaction time on yield of reaction

TABLE 3 indicates that the result of reaction which carried out on wide span of period. The plot of reaction time versus yield of 4, 6-dihydroxy 2-methyl pyrimidine (Figure 7), reveals that there is no significant change in yield from 0.5 to 2h and from 4 to 6h. Maximum 85% yield is obtained after 3 hours of reaction. The product purity was confirmed by the spectroscopic tools and also by elemental analysis. Optimization study helped reducing the reaction time from 5h to 3h, which significantly reduced the operational cost as well, improved the yield.

This optimized process was carried out at intermediate scale (500 g of acetamidinium chloride) in a jacketed glass reactor of 10L volume. The reactor was equipped with hot water circulator and double coil condenser (chilled water circulated) for reflux and agitator assembly containing four-blade turbine through variable frequency drive. The temperature of reaction and utilities were monitored and controlled automatically. The product obtained also met the quality and yield as laboratory product.

4. CONCLUSIONS

A systematic study on process chemistry of 4, 6-dihydroxy-2-methylpyrimidine has been carried out. Influence of various process parameters on the yield have been studied and this study reports optimized process for the economic production of 4, 6-dihydroxy-2-methylpyrimidine. The optimized process uses inexpensive dry methanol (0.2% max. moisture) instead of absolute ethanol as reaction medium and also minimizes the overall reaction time and process cost. The change in these parameters also led to the significant improvement in yield (85%) of 4, 6-dihydroxy-2-methylpyrimidine without loosing its quality.

5. ACKNOWLEDGMENTS

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