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# The Green Synthesis of 6-amino-5-cyano-4-phenyl-2-Hydroxy and Mercapto Pyrimidine Derivatives

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**Abstract:** *The simple, quick, green and efficient method for the synthesis of 6-amino-5-cyano-4-phenyl-2-mercapto pyrimidine and its hydroxyl derivatives using $CdFe_2(C_4H_4O_6)_35H_2O$. This new procedure is much more efficient, apart from its simplicity; the important advantage of the present procedure is the ability to tolerate variation in all the three components reactions. To the best of our knowledge, this is one of the quickest, economical, and simple alternatives towards the synthesis of 6-amino-5-cyano-4-phenyl-2-mercapto pyrimidine. Ease of separation of pure product, selectively and in high yields in comparison to the two-step strategies, are a few of the unique features of this method.*

**Keywords:** Cadmium Doped Iron Tartrate, 6-Amino-5-Cyano-4-Phenyl-2-Hydroxy and Mercapto Derivatives of Pyrimidine.

## I. INTRODUCTION

Pyrimidine is an aromatic nitrogen atom containing heterocyclic compound, it is also generalized as diazines due to presence of two nitrogen atom in six membered rings. The two nitrogen atoms are present at 1,3-position and it has wide range in nature. The structure of pyrimidine prominently found in nucleic acid and bases of RNA and DNA like cytosine, thiamine and uracil. In DNA and RNA these bases forms hydrogen bonds with their complementary purines. In DNA the purines adenine and guanine pairs up with the thymine and cytosine (Fig 1.1) respectively, whereas in RNA adenine and guanine pairs up with uracil and cytosine respectively. These hydrogen bonding were explained by very well-known classical Watson and Crick model.[1]

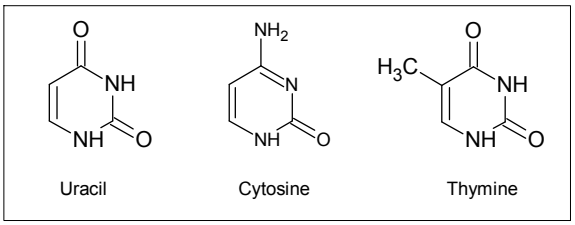


Figure 1.1

Pyrimidine has been also found in many synthetic drugs like barbiturates and HIV drug-zidovudine. Heterocyclic molecules are of biological interest due to their potential physical and chemical properties. Among these pyrimidine compounds occupy a unique position in pharmaceutical chemistry, as they are component of nucleic acids. The important pyrimidine compounds have diverse application as antibacterial[2,3] antifungal[4], antiviral[5], analgesic[6-8], antihypertensive, calcium channel blocker[9-11], antioxidants[12], anti-inflammatory[13-15], antiulcer, antagonist and anti-tumor agent[16].

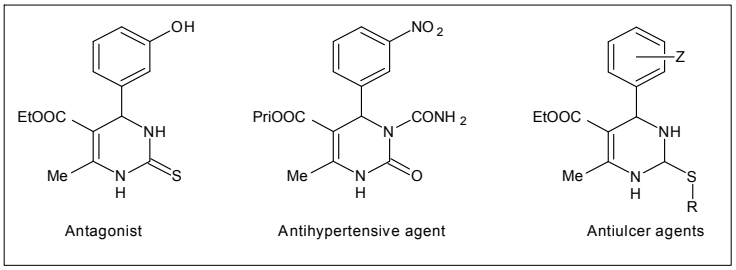


Figure 1.2

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## II. EXPERIMENTAL

The melting points were determined on an electrothermal apparatus and the temperature was not calibrated. IR spectra were recorded as thin films on KBr using Spectrum 400 spectrophotometer. The $^{13}$CNMR spectra were recorded on a Bruker AVANCE NEO 500 MHz NMR spectrometer. Sample solution was prepared in DMSO containing tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a Water S, Q-TOF MICROMASS (ESI-MS) at 70 eV.

All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled.

**General procedure for the synthesis of pyrimidine derivatives**

In 100 ml round bottom flask, aromatic aldehyde (1 mmol), malononitrile (1 mmol) and urea/thiourea (1 mmol) was stirred well in water followed by addition of $CdFe_2(C_4H_4O_6)_35H_2O$. Then the reaction mixture was refluxed using oil bath for about 45 minutes. The completion of reaction was monitored by silica coated TLC. The resulting reaction mixture was poured on 50 ml crushed ice by continuously stirring the mixture, then solid product was filtered, washed with ether, dried and recrystallized by using ethyl alcohol.

The catalyst was prepared by given procedure of coprecipitation which were reported earlier and similar complexes were used to synthesize heterocyclic compounds [17-18].

**Analytical Data of Some Important Compounds**

**6-amino-5-cyano-4-(4-Chloro)-phenyl-2-hydroxy pyrimidine**

$^1$H-NMR ($CDCl_3$, 200 MHz): 1.73 (s, 2H –$NH_2$), 7.40-7.95 (m, 4H), 8.63 (s, 1H br.s); $^{13}$C-NMR (DMSO, 500 MHz): 39.08, 39.58, 39.92, 82.07, 112.85, 113.90, 129.58, 129.92, 132.00, 138.95, 159.96; IR (KBr): 3430, 3027, 2849, 2220, 1604, 1567, 1609, 1368, 1320, 1276, 1183, 1018, 832, 606 cm$^{-1}$; MS (EI, 70 eV) m/z : 347.03 $[M+H]^+$.

**6-amino-5-cyano-4-(3-nitro)-phenyl-2-hydroxy pyrimidine**

$^1$H-NMR ($CDCl_3$, 200 MHz): 1.65 (s, 2H –$NH_2$), 7.20-7.44 (m, 4H), 8.08 (s, 1H br.s); $^{13}$C-NMR (DMSO, 500 MHz): 39.34, 39.76, 56.90, 82.32, 112.12, 113.37, 129.34, 129.45, 132.08, 138.46, 159.94; IR (KBr): 3454, 3027, 2834, 2212, 1645, 1571, 1616, 1339, 1368, 1244, 1110, 1025, 849, 645 cm$^{-1}$. MS (EI, 70 eV) m/z : 258.06 $[M+H]^+$.

**6-amino-5-cyano-4-(4-methoxy)-phenyl-2-hydroxy pyrimidine**

$^1$H-NMR ($CDCl_3$, 200 MHz): 1.62 (s, 2H –$NH_2$), 7.14-7.38 (m, 4H), 8.24 (s, 1H br.s), 3.47 (s, 3H); $^{13}$C-NMR (DMSO, 500 MHz): 39.15, 39.20, 41.65, 82.29, 114.06, 115.61, 129.97, 130.62, 132.40, 140.05, 158.14; IR (KBr): 3464, 3005, 2941, 2175, 1615, 1545, 1631, 1327, 1391, 1232, 1128, 1047, 885, 641 cm$^{-1}$. MS (EI, 70 eV) m/z : 243.08 $[M+H]^+$.

## III. RESULT AND DISCUSSION

A green, mild and efficient catalyst for the synthesis of 6-amino-5-cyano-4-phenyl-2-mercapto/hydroxy pyrimidine derivative by means of one-pot three component condensation Biginelli reaction of aromatic aldehydes (1 mmol), urea/thiourea (1 mmol) and malononitrile (1 mmol) in the presence of cadmium doped iron tartrate at 80°C is reported.(Scheme 1.1)

In the presence of Cadmium doped iron tartrate, reaction proceeds smoothly giving desire product in short time and good to excellent yield. The formation of product takes place when aromatic aldehydes were reacted with malononitrile to form arylmethylenemalononitrile, which reacts with urea or thiourea in later stage to give desire products.

In order to optimize the reaction conditions, the synthesis of 4-chloro benzaldehydemalononitrile and urea was used as model reaction. The effects of different amount of the catalyst on the reaction were studied and no product has been detected in the reaction without catalyst even after 5 hours. The best amount of catalyst was 0.01 gm the higher amount of the catalyst did not increase the yield of the products. The analysis has been shown in Table 1.1.

| Entry | Catalyst amount | Time | Yield |
|---|---|---|---|
| 1 | Catalyst Free | 120 | No product |
| 2 | 0.005 | 90 | 40 |

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|---|---|---|---|
| 3 | 0.01 | 90 | 88 |
| 4 | 0.01 | 45 | 88 |
| 5 | 0.02 | 45 | 85 |

**Table 1.1:** Optimization of reaction condition

The effect of temperature on the reaction was studied as well; no product has been detected at room temperature. The reaction was evaluated by changing temperature from 40-100°C. The best yield was obtained at 80°C.

To find out the efficiency and accountability of this three-component reaction, different aldehydes and urea/thiourea were tested. Aromatic aldehydes bearing either electron donating groups like methoxy or electron withdrawing like nitro were converted into corresponding products with good to excellent yields. The results are summarized in Table 1.2.

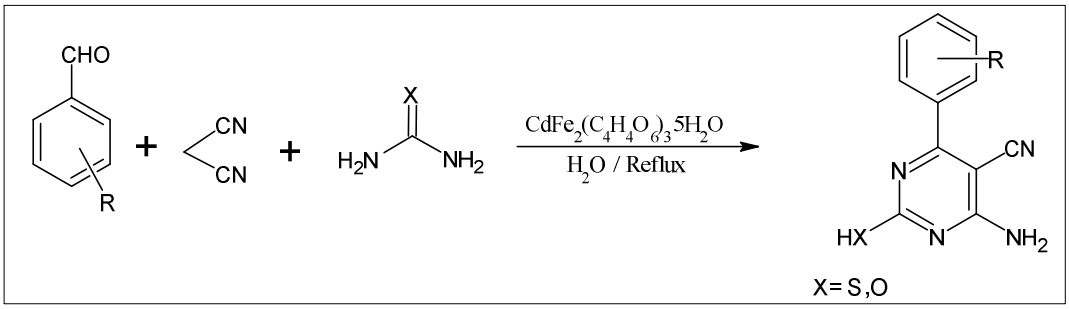
| Entry | Aldehydes | Products | Time (Min) | Yield (%) | M.P. (°C) | |
|---|---|---|---|---|---|---|
| | | | | | Obtained | Reported |
| 1 | Benzaldehyde | 1o | 45 | 92 | 180-182 | 179-181[21] |
| 2 | 3-nitro benzaldehyde | 2o | 45 | 90 | 230-232 | 228-230[21] |
| 3 | 4-methoxy benzaldehyde | 3o | 45 | 90 | 154-158 | 148-150[20] |
| 4 | 4-chloro benzaldehyde | 4o | 45 | 88 | 150-152 | 162-164[20] |
| 5 | 3,4-dimethoxy benzaldehyde | 5o | 45 | 90 | 170-172 | 167[19] |
| 6 | 4-nitro benzaldehyde | 6o | 45 | 90 | 210-216 | 221-223[21] |
| 7 | Benzaldehyde | 1s | 45 | 92 | 160-162 | 152-154[21] |
| 8 | 3-nitro benzaldehyde | 2s | 45 | 88 | 224-226 | 220[19] |
| 9 | 4-methoxy benzaldehyde | 3s | 45 | 90 | 154-156 | 150-152[21] |
| 10 | 4-chloro benzaldehyde | 4s | 45 | 92 | 138-140 | 135[21] |
| 11 | 3,4-dimethoxy benzaldehyde | 5s | 45 | 90 | 174-176 | 170-172[19] |
| 12 | 4-nitro benzaldehyde | 6s | 45 | 90 | 185-187 | 190-192[21] |

**Table 1.2:** Products obtained from respective aldehyde

Comparison of the catalytic activity of some catalyst reported in the literature for the synthesis of 6-amino-5-cyano-4-phenyl-2-mercapto/hydroxy pyrimidine derivatives are shown in Table 1.3. This study revealed that cadmium doped iron tartrate showed an extraordinary potential to be an alternative cheap, cost-effective, green, eco-friendly, efficient catalyst for this reaction. In addition, the use of solvent-free condition with excellent yields and short reaction time in the reaction with both urea and thiourea are the notable advantages of this present methodology.

| Entry | Catalyst | Conditions | Time (Min.) | Yield (%) | Reference |
|---|---|---|---|---|---|
| 1 | $P_2O_5$ | Reflux | 150 | 81 | [19] |
| 2 | $NH_4Cl$ | Reflux 110°C | 60 | 85 | [21] |
| 3 | $CdFe_2(C_4H_4O_6)_3 5H_2O$ | Reflux | 45 | 92 | This work |

**Table 1.3:** Comparison of catalyst




Scheme 1.1

## IV. CONCLUSION

In summary, a green protocol was studied for Biginelli synthesis of 6-amino-5-cyano-4-phenyl-2-mercapto/hydroxy pyrimidine derivatives via one pot, three component reaction of aldehydes, malononitrile and urea/thiourea in presence

of cadmium doped iron tartrate as catalyst under thermal and solvent free conditions. The notable advantages of the present methodology are low-cost, nontoxic catalyst, high catalytic activity, eco-friendly, excellent yield, short reaction times and environmentally benign nature.

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