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Citric acid catalyzed green and efficient synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitriles

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Abstract-Green and efficient methods have been developed for the synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitriles (**5**) by the reaction of benzaldehyde (**1**), ethyl cyanoacetate (**2**) and thiourea (**4**) using citric acid as an efficient, biodegradable and environmentally benign catalyst. Two methods, i.e., one-pot method and stepwise method have been employed for the synthesis of **5** using Biginelli reaction. The stepwise method involves the use of an intermediate, i.e., ethyl 2-cyano-3-phenylacrylate (**3**) and its reaction with thiourea. These two methods have been performed both in solvent media as well as in solvent free conditions. The merits of these developed methods are mild reaction conditions, lower reaction times, easy work up procedures and good yields.

Index Terms- Citric acid1, physical grinding2, one-pot synthesis3, solvent free conditions4, pyrimidines5.

1. INTRODUCTION

The biological significance of pyrimidine derivatives and numerous modifications upon this scaffold attracts the attention of chemists as an interesting area of study[1]. Pyrimidines occupy a distinct and unique place in medicine due to their diverse pharmacological activities such as anti cancer[2], anti viral[3], anti-HIV[4], anti bacterial[5], etc. One of the important reasons for their activity is due to the presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA and RNA[6].

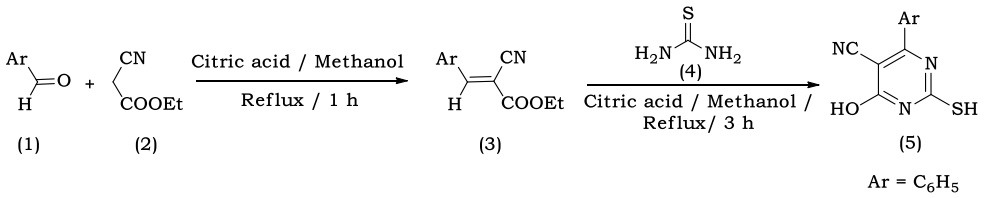
Biginelli reaction is one of the important multi component reaction for the synthesis of pyrimidines from ethyl cyanoacetate, aryl aldehyde and urea[7]. Li-Ying et al. prepared[8] the pyrimidine derivatives by using K_2CO_3 as a catalyst and ethanol as a solvent for 10 h under refluxing conditions. Murthy et al. reported[9] the synthesis of pyrimidine derivatives using $Mg(OMe)_2$ solution in refluxing ethanol for 5 h. Heba et al. reported[10] the synthesis of pyrimidine derivatives using methanol as a solvent and K_2CO_3 as a catalyst under refluxing conditions for 7 h. Stella et al. reported[11] the synthesis of pyrimidines in refluxing ethanol using piperidine as a catalyst for overnight.

Even though there are many reports for the synthesis of these pyrimidines, some of the above described methods are suffering from drawbacks like prolonged reaction times, usage of toxic and environmental unfavorable solvents, association of impurities and relatively low yields. Therefore, to overcome these limitations, the discovery of new, eco-friendly and easily available catalyst with high catalytic activity and short reaction time is still desirable. In this regard, citric acid keeps the potential of performing the role of ideal catalyst. There are reports in the literature on the use of citric acid as catalyst in organic synthesis[12-14] due to its non toxic nature, easy availability and for simple work up procedure. In recent years, considerable attention has been paid to reactions done under solvent-free conditions.[15-16] One of the areas of central attention in this field includes reactions between solids.[17-18] These reactions are not only of interest from economical point of view but also in many cases they offer considerable synthetic advantages in terms of yield, selectivity and simplicity of the reaction procedure. So it was thought of interest to study preparation of title compounds both in solvent media and also in solid free method using citric acid as an efficient catalyst.

2. RESULTS AND DISCUSSION

2.1. *Traditional method*

As shown in **scheme-1**, benzaldehyde (**1**) was treated with ethyl cyanoacetate (**2**) in methanol using citric acid as a catalyst under refluxing conditions for 1 h to yield ethyl 2-cyano-3-phenylacrylate (**3**). Further, the reaction of **3** with thiourea (**4**) using citric acid as a catalyst in refluxing methanol for 3 h resulted in the formation of a cyclized product, i.e., 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitrile (**5**).



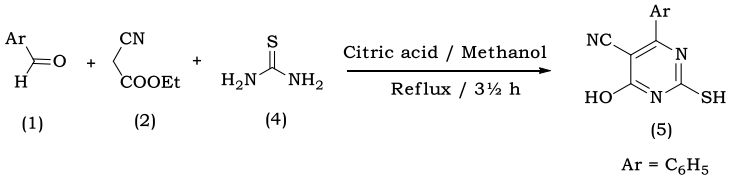
(1) (2) (3) (5)

Scheme. 1. Step-wise synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitriles (**5**)

Encouraging with the above result, it was thought of interest to synthesize the compound **5** in a one-pot reaction, since the same catalyst has been employed for both the steps in **Scheme-1**. Thus, equimolar amounts of benzaldehyde (**1**), ethyl cyanoacetate (**2**) & thiourea (**4**) were reacted together in a one-pot, using citric acid as a catalyst and methanol as a solvent under refluxing conditions for a period of 3½ h to give **5**. (**Scheme-2**).

The effect of catalyst has also been checked by carrying out the same reaction with other catalysts such as L-proline, sulfamic acid, pyridine, KOH, K_2CO_3 each in the solvent ethanol. (**Table 2**).

Thus, from the above optimization studies it was proved that the citric acid and ethanol combination found to be best choice over the other combinations. Thus, the above one-pot reaction of **1** with **2** & **4** in ethanol using citric acid as a catalyst to



(1) (2) (4) (5)

Scheme. 2. One-pot synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitriles (**5**)

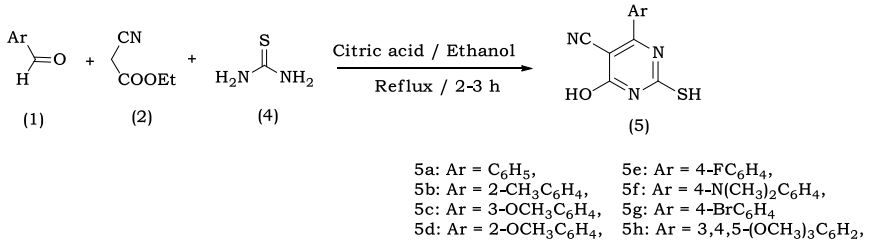
In order to know the effect of solvent, this one-pot reaction has been performed in different solvents. Among all the solvents used, ethanol was found to be the best solvent in terms of reaction time and product yield. (**Table 1**)

give **5** was found to be a general one and was extended to other benzaldehyde derivatives. (**Scheme-3)**

Table-1: Effect of solvent on the one-pot synthesis of at their reflux temperature

S.No.	Solvent	Catalyst (30 mol %)	Time (h)	Yield (%)
1	Methanol	Citric acid	3½	68
2	**Ethanol**	**Citric acid**	**2**	**77**
3	Isopropyl alcohol	Citric acid	4	61
4	Tetrahydrofuran	Citric acid	5	57
5	Dioxane	Citric acid	4½	60
6	Acetonitrile	Citric acid	6	54
7	Benzene	Citric acid	9	43
8	Water	Citric acid	10	Nil

S.No.	Solvent	Catalyst	Time (h)	Yield (%)
1	Ethanol	No catalyst	24 h	Nil
2	Ethanol	L-proline	4 h	60
3	Ethanol	Sulfamic acid	5 h	56
4	Ethanol	Piperidine	9 h	67
5	Ethanol	KOH	8 h	50
6	Ethanol	K_2CO_3	10 h	65
7	Ethanol	No catalyst	24 h	Nil
8	Ethanol	L-proline	4 h	60



Scheme. 3. One-pot synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitriles (**5**) in ethanol

2.2. *Solvent free method*

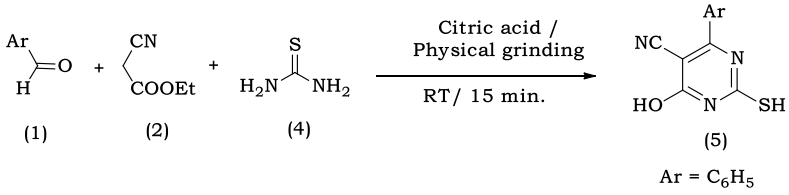
With the above positive results obtained in solution phase, it was thought of interest to synthesize the title compounds under solvent-free conditions. Thus, equimolar amounts of benzaldehyde (**1**), ethyl cyanoacetate (**2**) & thiourea (**4**) were grounded together in a mortar and pestle, using citric acid as a catalyst at RT for 15 min. The reaction was monitored by TLC and interestingly, the reactants were completely consumed to give the product. Subsequent work-up of the reaction mass yielded a product that is identical with **5a**, obtained in solution phase method, in all respects with mp, mmp. It was found that above reaction did not proceed in the absence of citric acid even after grinding mixture for 1-2 h. Thus it appears that citric acid acts as an efficient catalyst which makes the reaction to occur much faster. (**Scheme-4)**

The effect of catalyst on the solid state reaction has also been checked by carrying out the physical grinding reaction with other catalysts such as L-proline, sulfamic acid, pyridine, KOH, K_2CO_3 each independently. (**Table 3**).

From the above optimization data carried out in solid phase method, sulfamic acid was found to be better choice over other catalysts, but still it was not superior to citric acid.

Thus, this one-pot solid-phase reaction between **1, 2 & 4** using citric acid as a catalyst, has been found to be a general one and was extended to other benzaldehyde derivatives. The products thus obtained were found to be identical with the ones prepared in solvent media. (**Scheme-5)**

This solid state synthesis was also successfully carried out in step-wise method using

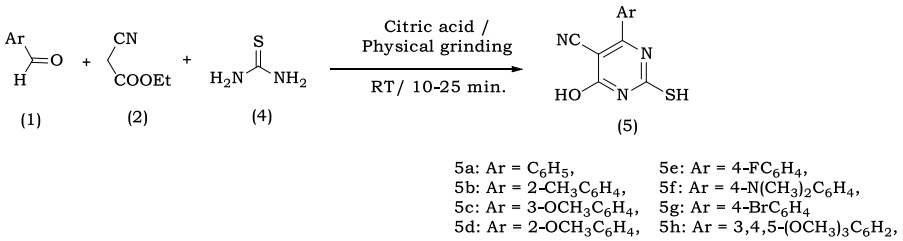


Scheme. 4. Solvent free one-pot synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitrile (**5**)

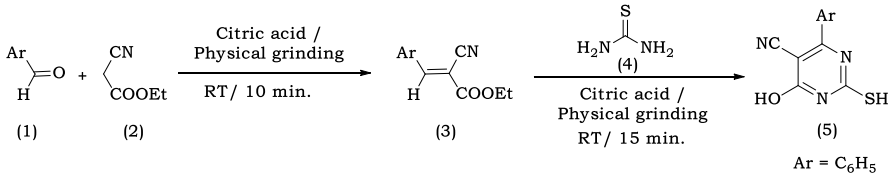
citric acid as an effective catalyst. **Scheme-6.**

Table-3: Effect of catalyst on the one-pot synthesis of **5** in solid state method

S.No.	Catalyst	Time (min)	Yield (%)
1	No catalyst	60 min	Nil
2	L-proline	30 min	64
3	Sulfamic acid	25 min	68
4	Piperidine	40 min	37
5	KOH	35 min	33
6	K_2CO_3	40 min	39



Scheme. 5. Solvent free one-pot synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitrile (**5**)



Scheme. 5. Solvent free step-wise synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitrile (**5**)

Table-3: Comparison data for the one-pot preparation of **5** in solvent media and solvent free conditions

S.No	Starting Materials used	Product obtained	Melting Point (°C) [Ref]
1	**1a**: Ar=C_6H_5, **2** & **4**	**5a:** Ar = C_6H_5	238-240[9]
2	**1b**: Ar=2-$CH_3C_6H_4$, **2** & **4**	**5b:** Ar = 2-$CH_3C_6H_4$	210-212[19]
3	**1c**: Ar=3-$OCH_3C_6H_4$, **2** & **4**	**5c:** Ar = 3-$OCH_3C_6H_4$	130-132[19]
4	**1c**: Ar=2-$OCH_3C_6H_4$, **2** & **4**	**5c:** Ar = 2-$OCH_3C_6H_4$	215-217[20]
5	**1d**: Ar=4-FC_6H_4, **2** & **4**	**5d:** Ar = 4-FC_6H_4	235–236[21]
6	**1e**:Ar=4-$N(CH_3)_2C_6H_4$, **2** & **4**	**5e:** Ar = 4-$N(CH_3)_2C_6H_4$	230–232[21]
7	**1f**: Ar=4-BrC_6H_4, **2** & **4**	**5f:** Ar = 4-BrC_6H_4	225–226[21]
8	**1g**: Ar=3,4,5-$(OCH_3)_3C_6H_2$, **2** & **4**	**5g:** Ar = 3,4,5-$(OCH_3)_3C_6H_2$	245–247[21]

From **Table-4**, it can be observed that the reaction which required 2-3 h by the solvent method, was completed within 10-25 min. by the physical grinding and yields have been remarkably improved.

3. EXPERIMENTAL SECTION

3.1: *One pot synthesis of 5 using ethanol as a solvent (General procedure):*

A mixture of **1** (10 mM), **2** (10 mM), **4** (10 mM), citric acid (30 mol%) and ethanol (30 ml) was refluxed for 2-3 h. The progress of the reaction was monitored on

TLC. After completion of reaction, as indicated by the disappearance of starting materials, the mixture was poured into ice-cold water (30 ml). The separated solid was filtered, washed with water (2x30 ml) and dried. The crude product was recrystallized from suitable solvent to obtain pure **5**.

3.2: ***One pot synthesis of 5 in physical grinding method (General procedure):*** A mixture of **1** (10 mM), **2** (10 mM), **4** (10 mM) and citric acid (30 mol%) was taken into a mortar and grounded with pestle. The progress of the reaction was monitored by TLC. After completion of the reaction 20 mL of distilled water was added to the reaction mixture, separated solid was filtered out and washed with cold water (2x20 mL) and dried to obtain crude product. The latter were recrystallized from suitable solvent to obtain pure **5**.

4. CONCLUSION: In conclusion, we have developed simple and efficient methods for preparation of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitriles (**5**) in solution phase, as well as under solvent-free conditions (simple physical grinding in mortar and pestle) using citric acid as a catalyst. The solvent free system gave promising results and citric acid appeared to be the best catalyst for this reaction. It appears from this study that solid phase synthesis (physical grinding) is very efficient method which gave better yields, quality of products in less reaction time, over the conventional methods (solution phase) and we have avoided the use of energy in the form of heating by conducting the experiment at room temperature.

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