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An Organic Acid- 5-Sulfosalicylic Acid : a Metal Free Catalyst for Synthesis of Dihydropyrimidin-2(*1H*)-ones under No Solvent Condition

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Abstract

We have been developed an highly functionalized protocol for multicomponent synthesis of Dihydropyrimidin-2(*1H*)-ones via Biginelli reaction using aromatic aldehyde, ethyl acetoacetate and urea heating at 90°C. The reaction is worked out under solvent free condition and catalyzed by organo-catalyst 5-sulfosalicylic acid. The protocol exhibit several key features like use of non-hazardous, low cost, recyclable and metal free catalyst in addition to shorter reaction time, high yield, simple and clean work-up procedure. The product were confirmed by instrumental analysis.

Keywords: *Biginelli reaction; 5-sulfosalicylic acid; non-hazardous; low cost; recyclable, metal free catalyst*.

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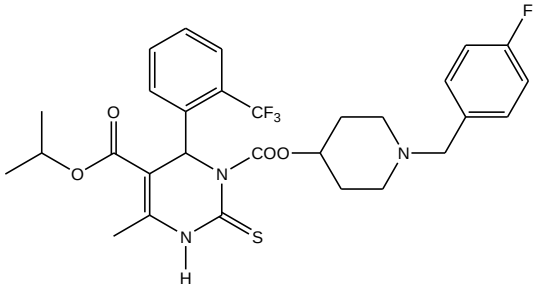
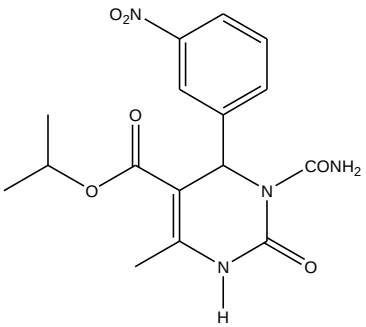
1. Introduction

Heterocyclic compounds are important class of organic compounds which have led to medicinal and industrial development of society [1]. Alkaloids are nitrogen containing heterocycles having natural origin from plant source and are most active molecules used for treatment of various diseases [2]. An enormous number of nitrogen containing heterocyclic compounds are identified and this number increases day by day. Multicomponent reactions (MCRs) are special supreme pathway in the field of heterocyclic compound synthesis of medicinally potent framework. Now a days, many researchers come across with MCRs as gain in atom economy, high efficiency, high yield, target specificity and especially one pot synthesis. The multicomponent reactions are referred as synthesis of one pot, convergent chemical reactions from two or more than starting materials. [3-4]. The selectivity and yield of MCRs are highly sensitive towards choosing of proper catalyst, thus selection of appropriate catalyst possess properties such as mild, efficient and inexpensiveness for organic synthesis of biological and pharmaceutical active analogue has great importance. So MCRs are most sustainable, valuable and universal admissible tool which encourage organic researchers for the design and development of medicinally relevant scaffolds.

The dihydropyrimidinone and its derivatives exhibit crucial biological activities such as antibacterial [5], antifungal [6], antiviral [7], anticancer [8], anti-diabetic [9], anti-ulcer [10], anticonvulsant [11] and calcium channel blockers [12]. Few years ago, some dihydropyrimidinones were developed among which SQ 32926 and SQ 32547 have been identified as anti-hypertensive agents. [13] (Fig. 1.) they are orally active and highly potent in nature. The dihydropyrimidinone-azo pyridone dyes are have been synthesized exhibit interesting anticancer activity [14].



SQ32547



SQ32926

Fig. 1

Italian chemist Pietro Biginelli was first to report the one pot multicomponent synthesis of pharmaceutically active dihydropyrimidinones by condensation of aromatic aldehyde, urea and ethyl acetoacetate reflux in ethanol under strong acidic condition of conc. HCl [15-16]. Due to medicinally importance of Biginelli adducts, many of researchers reported numerous procedures with several modification in last decade for their synthesis such as Bent-TPA [17], TEAA [18], N,N-diethyl-N-sulfoethanaminium hydrogen sulfate [19], Silicotungstic acid anchored to Amberlyst-15 [20], PPh_3 [21], Bent-PMA [22], Fe_3O_4@SiO_2-imid-PMA [23], HPVAC-20 [24], Fe-C-O-Mo alloy [25], H_3PO_2 [26], Eosin Y [27], PMO-Py-IL [28], Bent-TSA [29], H_3PO_4 [30], CAS [31], L-proline nitrate [32], Amberlyst 15

DRY [33], PTA@MIL-101 [34], $ZrCl_4$ [35], MOFs [36]. Although, in spite of their potential utility, some of these protocols travel from one or many disadvantages like as inadequate yield, severe reaction condition, use of toxic organic solvents or prolonged reaction time, immoderate use of catalyst, formation of side products. Further organic reaction using metal free catalyst and solvent free condition have attracted much attention from researchers, especially in view of green chemistry. [37-39]. The several organic acids plays crucial role as a catalyst in synthesis of biologically active heterocyclic compounds [40-43]. The use of little organic molecules as an organocatalyst is highly acceptable in the field of organic synthesis. The organocatalyst exhibit better advantages over metal catalyst such as lower activation energy barrier, more stability, eco-friendliness, inexpensiveness, lower toxicity, easy handling, stable in air and moisture. They avoid the generation of metallic waste and metal trace in the product [44]. So these aspects motivate us which results in development of new protocol for synthesis of dihydropyrimidinones using 5-sulpho salicylic acid as an metal free organic acid catalyst. The 5-sulpho salicylic acid bears impressive sulphonic acid group which exhibit acidic nature. It is strong Bronsted acid as it donates proton and form more stabilized aromatic anion. (Fig. 2). The 5-sulpho salicylic acid used for determination of protein content in urine.[45], identification of sugars on TLC [46], as an chelating agent [47], as a redox indicator [48]. The 5-sulpho salicylic acid is an organic acid catalyst possesses properties like bio-degradability, stability, non-toxicity, water solubility and superior catalytic activity which promote us to select it as a catalyst for synthesis of dihydropyrimidinone and its derivatives under solvent free condition.

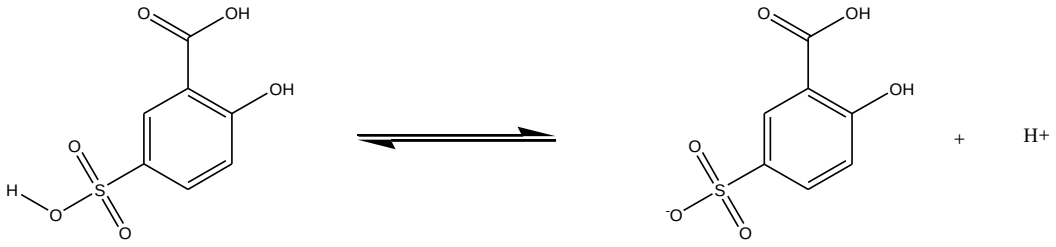


Fig. 2

5- sulpho salicylic acid

Conjugate base

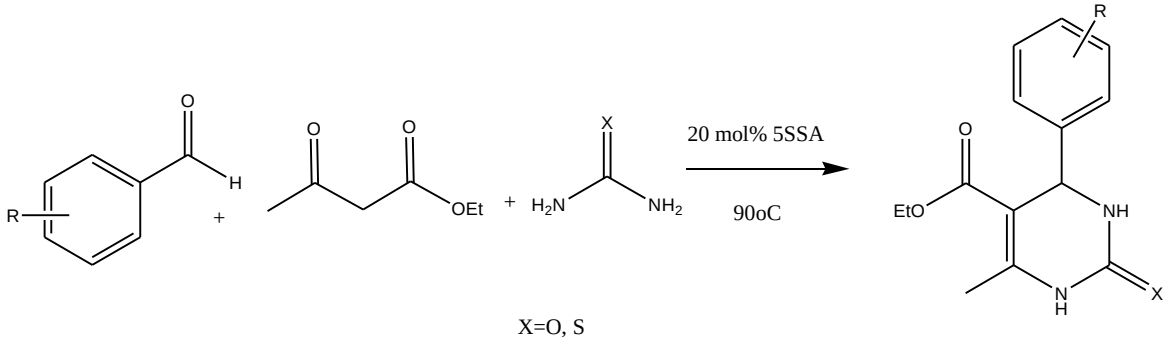
2. Materials and Methods

All the chemicals were in analytical grade and purchased from commercial suppliers and used without further purification. The melting point were recorded on digital melting/boiling point apparatus of Labtronics make which found uncorrected and compared with reported literature. The reaction progress were monitored by thin layer chromatography using Merk prepared precoated plates of TLC silica gel 60 F_{254} using 30% ethyl acetate in hexane as mobile phase. Visualization was made with UV light chamber (254 or 365nm). LCMS were recorded indicates molecular ion peak. The ^{1}H NMR spectra were recorded on Bruker- 500 MHz spectrometer in $CDCl_3$ solvent using TMS as an internal standard and chemical shift is given as a delta. The percentage yield was given for all compounds.

General procedure for the synthesis of Dihydropyrimidin-2(1H)-ones Derivatives:-

In a 50 ml round bottom flask a mixture of aromatic aldehyde (1mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) was taken in presence of 20 mol%

5-sulpho salicylic acid (Fig.3). The reaction mixture was heated for 30 min. at 90^{o}C. After the completion of reaction as indicated by TLC, reaction mixture was allowed to cool at room temperature and crushed ice was added and stirred until a free-flowing solid generated in the RB flask. The resultant solid was filtered through Buchner washed with water followed by hexane and then dried. The crude product was purified by recrystallization using ethanol solvent. The recovery of catalyst were carried out by evaporating the aqueous layer (filtrate) and it has been reused as a catalyst for next four times.

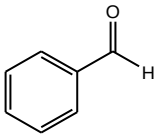
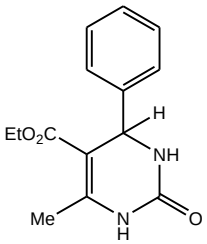


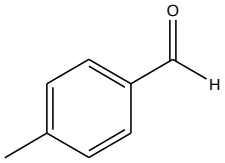
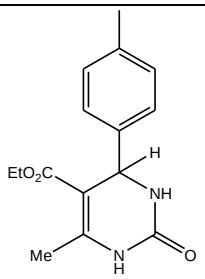
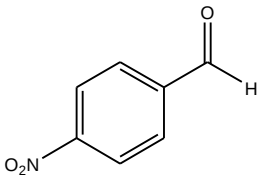
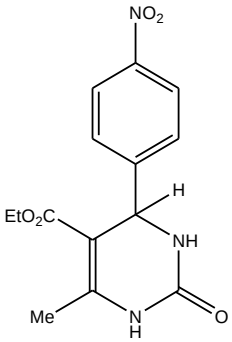
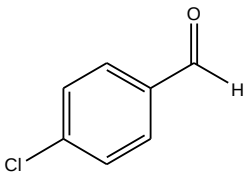
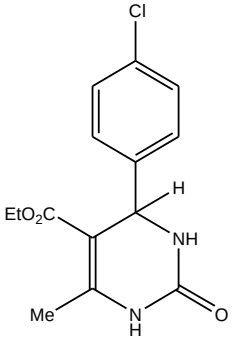
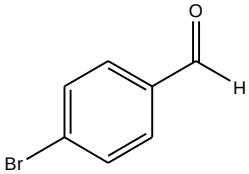
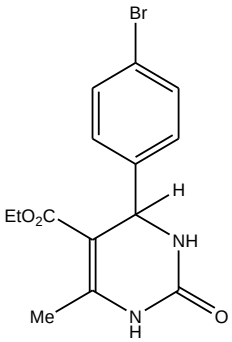
X=O, S

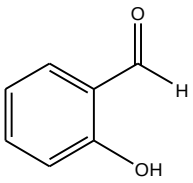
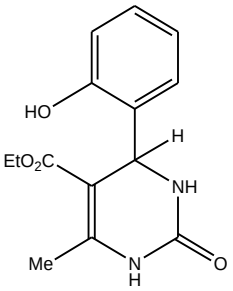
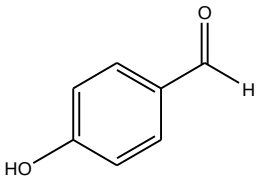
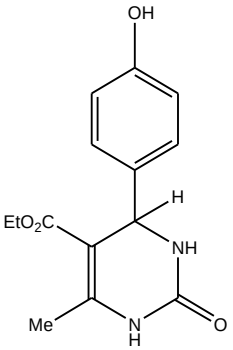
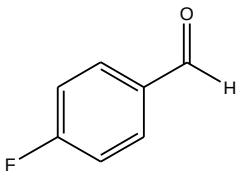
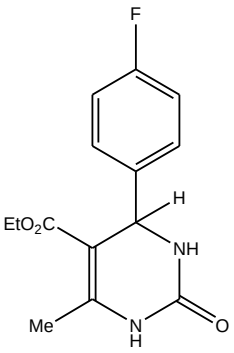
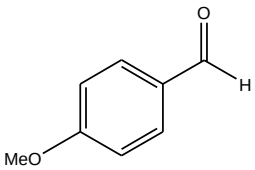
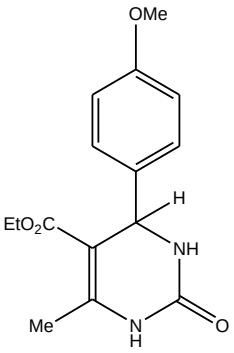
Fig. 3

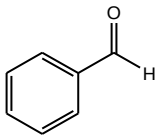
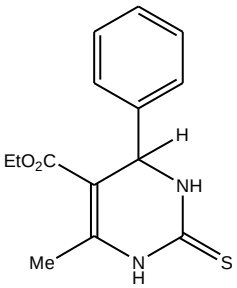
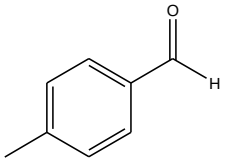
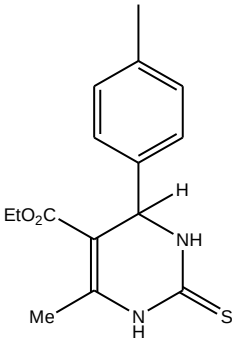
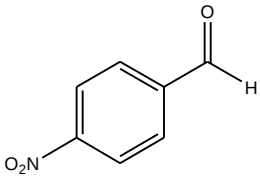
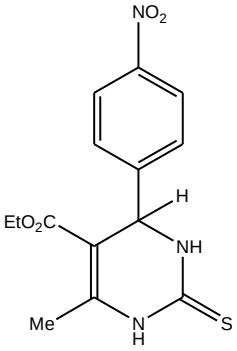
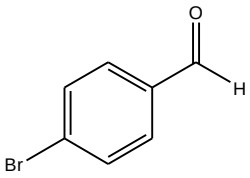
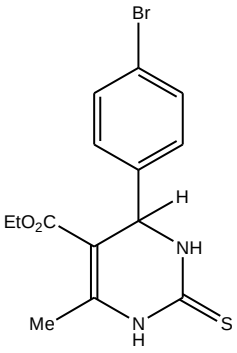
We decorate the above protocol for different substituted aromatic aldehyde, ethyl acetoacetate and urea in presence of a catalytic amount of 5-sulpho salicylic acid (20 mol%) with excellent yield of corresponding Dihydropyrimidin-2(1H)-ones Derivatives. In general all reaction were completed between 40 to 60 min.at 90^{o}C and product with Dihydropyrimidin-2(1H)-ones derivatives were obtained in 75-95 % yields. (Table 1.). The compounds were confirmed by their ^{1}H NMR analysis.

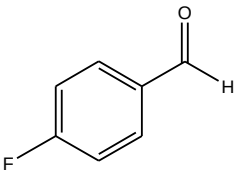
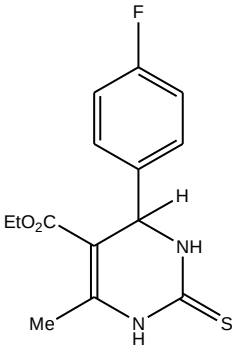
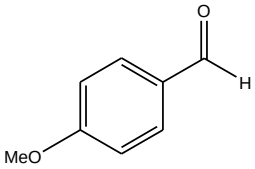
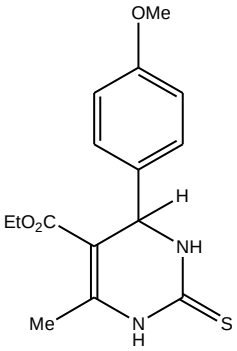
Table 1: Synthesis of Dihydropyrimidin-2(1H)-ones derivatives using different substituted aromatic aldehyde, ethyl acetoacetate, and urea using phosphoric acid[a].

Entry	**Aromatic aldehyde**	**DHPM derivatives**	**Yield[b] %**	**Time in min**	**Meling Point ^{o}C (reported)[c]**
1		 4a	90	45	203-205 (201-203)

2		 4b	92	50	215-216 (217-219)
3		 4c	90	40	214-216 (211-213)
4		 4d	85	60	208-210 (212-214)
5		 4e	90	50	206-208 (208-209)

6		 4f	85	60	204-206 (201-203)
7		 4g	88	55	233-234 (235-236)
8		 4h	86	50	181-183 (178-180)
9		 4i	92	45	202-204 (198-200)

10		 4j	90	45	205-206 (207-209)
11		 4k	92	50	191-193 (187-190)
12		 4l	94	40	218-220 (220-222)
13		 4m	85	60	190-192 (193-195)

14		 4n	84	55	205-206 (201-203)
15		 4o	90	50	215-216 (218-220)

[a]reaction condition: aromatic aldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) was taken in presence of a 5-sulpho salicylic acid (10 mol%). [b]yield refer to isolated product. [c]reported melting point

Analytical Data of Compound:-

4a:5-Ethoxycarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (t, 3H, J = 7.15 Hz, CH_3), 3.97 (q, 2H, J = 7.15 Hz, OCH_2), 2.24 (s, 3H, CH_3), 7.21–7.34 (m, 5H, ArH), 5.13 (d,1H, J = 3.3 Hz, CH), 9.18 (s, 1H,NH), 7.73 (s, 1H, NH)

MS (m/z): 260 (M+)

4b:5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (t, 3H,J = 6.7 Hz, CH_3), 3.95 (q, 2H, J = 6.7 Hz, O$\underline{CH_2}$), 2.22 (s,3H, CH_3), 2.30 (s, 3H, Ar-CH3), 7.23 (d, 2H, J= 8.6Hz, ArH), 7.12 (d, 2H, J= 8.6 Hz, ArH), 9.20 (s, 1H, NH),7.73 (s, 1H, NH)

MS (m/z): 307 (M+)

4c: 5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (t, 3H, J=7.5 Hz, CH_3), 4.10 (q, 2H, J=7.5 Hz, OCH_2), 2.37 (s, 3H, CH_3), 7.51 (d, 2H, J=7.0 Hz, ArH), 8.19 d, 2H, J=7.0 Hz, ArH), 5.53 (d, 1H, J=3.0 Hz, CH), 7.32 (s, 1H, NH), 5.62 (s, 1H, NH)

4e:5-Ethoxycarbonyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (t, 3H, J = 6.9 Hz, CH_3); 3.93 (q, 2H, J = 6.9 Hz, OCH_2), 2.20 (s, 3H,CH3), 7.48 (d, 2H, J =8.1 Hz, ArH), 7.14 (d, 2H, J = 8.1 Hz, ArH), 5.07 (d, 1H, J =2.8 Hz, CH), 9.20 (s, 1H, NH), 7.73 (s, 1H, NH)

MS (m/z): 339 (M++)

4g:5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

^{1}H NMR (400 MHz, DMSO-d6):δH 9.06 (s, 1H, NH), 7.57 (s, 1H, NH), 7.02 (d, 2H,ArH), 6.67(d, 2H, ArH), 5.03 (d, 1H,J = 2.9 Hz, CH), 3.97(q, 2H, J = 7.15 Hz, OCH2), 2.22 (s, 3H, CH3),1.09 (t, 3H, J= 7.15 Hz, CH3)

MS (m/z): 277 (M+H).

4h:5-Ethoxycarbonyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 (t, 3H, J=7.0 Hz, CH_3), 4.08 (q, 2H, J=7.0 Hz, OCH_2), 2.35 (s, 3H, CH_3), 7.20 (d, 2H, J=7.0 Hz, ArH), 6.83 (d, 2H, J=7.0 Hz, ArH), 5.33 (d, 1H, J=3.0 Hz, CH), 8.17 (s, 1H, NH), 7.53 (s, 1H, NH)

4i:5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (t, 3H, J=6.8 Hz, CH_3), 3.96 (q, 2H, J=6.8Hz, OCH_2), 2.23 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 7.15-6.84 (m, 4H, ArH), 9.14 (s, 1H, NH), 7.66 (s, 1H, NH)

4j: 5-Ethoxycarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (t, 3H, J=7.0 Hz, CH_3), 4.00 (q, 2H, J=7.0 Hz, OCH_2), 2.28 (s, 3H, CH_3), 7.19-7.35 (m, 5H, ArH), 5.16 (d, 1H, J=3.5 Hz), 10.33 (s, 1H, NH), 9.64 (s, 1H, NH)

4k:5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (t, 3H, J=7.0 Hz, CH_3), 4.00 (q, 2H, j=7.0 Hz, OCH_2), 2.25 (s, 3H, CH_3), 2.27 (s, 3H, Ar-CH_3), 7.07-7.16 (m, 4H, ArH), 10.27 (s, 1H, NH), 9.58 (s, 1H, NH)

4l: 5-Ethoxycarbonyl-4-(4-nirtophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (t, 3H, J=7.1 Hz, CH_3), 4.0 (q, 2H, J=7.1 Hz, OCH_2), 2.30 (s, 3H, CH_3), 7.45-8.25 (m, 4H, ArH), 5.26 (s, 1H, CH), 10.40 (s, 1H, NH), 9.62 (s, 1H, NH)

4m:5-Ethoxycarbonyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (t, 3H, J=7.0 Hz, CH_3), 4.10 (q, 2H, J=7.0 Hz, OCH_2), 2.36 (s, 3H, CH_3), 7.16-7.45 (m, 4H, ArH), 5.36 (d, 1H, J=3.0 Hz, CH), 8.11 (s, 1H, NH), 7.64 (s, 1H, NH)

4o:5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

^{1}H NMR (500 MHz, $CDCl_3$): δ1.17 (t, 3H, J=7.5 Hz, CH_3), 4.08 (q, 2H, J=7.5 Hz, OCH_2), 2.35 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.98-7.30 (m, 4H, ArH), 5.39 (d, 1H, J=2.5 Hz, CH), 7.47 (s, 1H, NH), 5.51 9s, 1H, NH)

3. Results and Discussion

In order to screen most relevant organo catalyst for synthesis of dihydropyrimidinone and its derivatives, we pick out an model condensation reaction of 4-nitro benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol), urea (1.2 mmol) using various organic acid catalyst (10 mol%) solvent free condition and at 90^0C temperature for different time. It was observed that 5-sulpho salicylic acid as an organo catalyst provide better result among all other catalyst. (Table. 2 Entry 6). From this observations, we performed some reaction by varying concentration of 5-sulpho salicylic acid as an organo catalyst from 0, 5, 10, 15, 20 and 25 mol%. It was

notice that catalyst concentration shows remarkable effect on yield of desired product and therefore we assure 20 mol% of catalyst amount was enough sufficient for synthesis of dihydropyrimidinone with better yield. (Table. 3, Entry 5).

Table. 2: Screening of organo catalyst for synthesis of 4C[a].

Entry	Organo catalyst (10 mol%)	Time in min.[b]	Yield (%)[c]
1	Phenyl acetic acid	80	50
2	Phenyl salicylic acid	75	55
3	Tannic acid	75	60
4	Lactic acid	70	65
5	Thio glycolic acid	70	70
6	**5-sulpho salicylic acid**	**60**	**80**

[a]Reaction condition: 4-nitro benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol), urea (1.2 mmol), solvent free and at 90^0C temperature [b]Time in min. [c]Isolated yield

Table. 3: Optimization of catalyst concentration[a].

Entry	5-sulpho salicylic acid conc.	Time in min.[b]	Yield (%)[c]
1	0 mol%	60	trace
2	5 mol%	60	10
3	10 mol%	70	15
4	15 mol%	70	40
5	**20 mol%**	**40**	**90**
6	25 mol%	40	90

[a]Reaction condition: 4-nitro benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol), urea (1.2 mmol), solvent free and at 90^0C temperature [b]Time in min. [c]Isolated yield

Recyclability of catalyst:-

The recyclability of catalyst was also studied under optimized reaction condition. The catalyst is water soluble and easily recovered under vacuum by removing solvent, it is then dried and used for next run. It was observed that catalyst can be reused for four consecutive times as indicated in graph with slight decrease in yield. (Fig. 4)

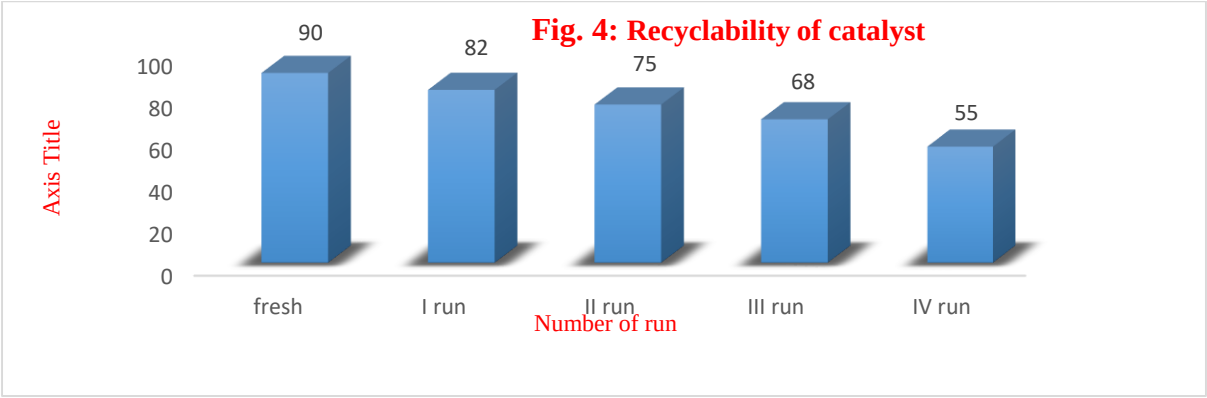


Fig. 4: Recyclability of catalyst

4. Conclusions

In the present work, we have developed 5-sulfosalicylic acid as an organo catalyst for multicomponent synthesis of Dihydropyrimidin-2(*1H*)-ones via Biginelli reaction using aromatic aldehyde, ethyl acetoacetate and urea heating at 90ºC. The reaction progress takes place under solvent free and metal free condition. The protocol exhibit several key features like use of non-hazardous, low cost chemicals. The shorter reaction time, high yield, simple and clean work-up procedure are important aspects of this work. The organo catalyst 5-sulfosalicylic acid is easily available, safe to handle, water soluble as well as recovered and reused effectively.

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Conflicts of Interest

The authors declare no Conflicts of Interest.

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