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Resorcin[4]arene Sulfonic Acid as a New and Efficient Organocatalyst for the One-Pot Synthesis of Fused Pyrimidine Derivatives

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Abstract: The synthesis of fused pyrimidine scaffolds has been streamlined into a single pot and effective technique that uses recyclable resorcin[4]arene tetrasulfonic acid as an organo-catalyst in a solvent-free environment. Excellent yields are obtained when using resorcin[4]arene tetrasulfonic acid as a reusable organo-catalyst in synthesizing fused pyrimidine derivatives. The method is valuable and eco-friendly because of its selectivity, nontoxicity, high yield, and recyclable catalyst, eliminating chromatographic purification processes.

Keywords: Organocatalyst; Resorcin[4]arene tetrasulfonic acid; Pyrimidine derivatives.

1. Introduction

Multi-component reactions have emerged as powerful tools in the pharmaceutical industry due to their plausibility for generating molecular diversity in a single synthetic step [1-4]. Among the multi-component reactions, preparing heterocyclic compounds in environmentally friendly conditions is essential [5-8]. Biginelli reaction is crucial for synthesizing pyrimidine derivatives using diketone, aldehydes, and urea. This moiety proved promising biological activity: antihypertensive [9], antibacterial [10], alpha-1a adrenoceptor-selective antagonists [11], antioxidant agents [12], and anticancer agents such as monstrol (**3**) [13]. Considering that coumarin derivatives theme self-possess a variety of pharmaceutical properties [14], their blend with a pyrimidine fragment could give rise to compounds with enhanced biological activity. Fused pyrimidine derivatives work a vital role in medicinal and synthetic organic chemistry, generally due to their wide range of biological activities [15-16], remarkably as calcium channel blockers like the SQ-32926 (**1**) (Fig. 1), the structurally related marine alkaloids batzelladine (**2**) displayed to be the first low molecular weight natural products to prevent the binding of HIV gp-120 to CD4 cells, so offering new insights towards the development of AIDS therapy [17].

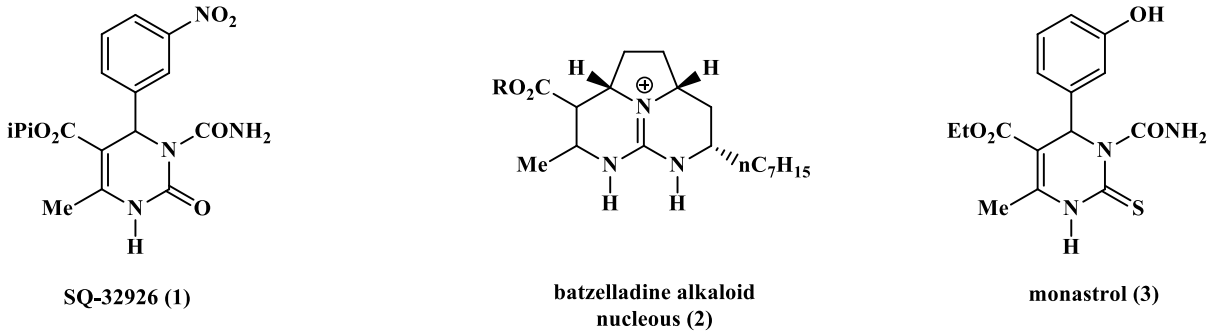

Figure 1. Structurally related some alkaloids

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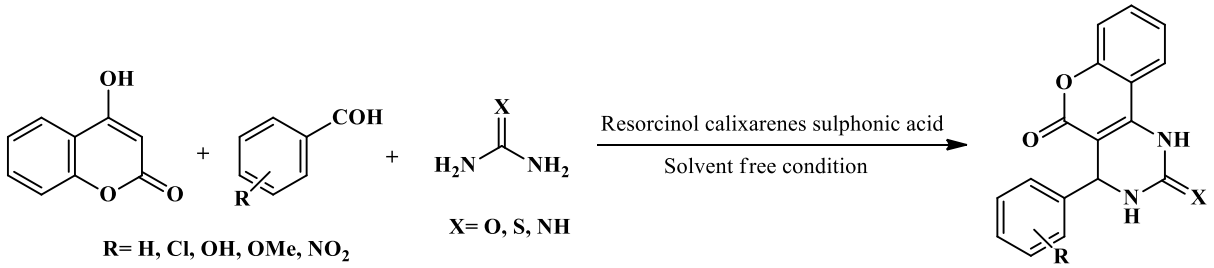
Although several synthetic strategies have been used to synthesize fused pyrimidine derivatives, most of these procedures have disadvantages, such as using expensive chemicals, severe reaction conditions, long reaction times, laborious isolation procedures, and side products. Eco-friendly catalysts are gaining popularity due to their low cost and low level of toxicity. Furthermore, improved selectivity is commonly seen, and the compounds can be easily extracted with high chemical purity using simple filtration, saving time and eliminating extensive extractive workup. An organo-catalyst, composed of organic molecules, is a catalyst that speeds up chemical reactions using a sub-stoichiometric quantity of an organic compound that is free of metal. Organo-catalysis receives greater interest because of its simple operation, low toxicity, low cost, selectivity, and high water and molecular oxygen trace tolerance. Apart from the main benefit of utilizing catalysts, which is their ability to create multi-component reactions through recycling and reusing organo-catalysts, other advantages are associated with their use. Organo-catalysts could, therefore, serve as an environmentally friendly form of catalysis than conventional catalysis. Supramolecular catalysts are a fast-growing field in supramolecular chemistry and catalysis benefits from advances in hydrogen bonding and supramolecular interaction.

The fused pyrimidine is synthesized mainly by a three-component coupling reaction of aromatic aldehydes, 4-hydroxy coumarins, and urea catalyzed by HCl, VCl_3, Montmorillonite K10 clay, silica gel, acidic alumina, and L-proline [17]. However, many of these procedures suffer from one or more drawbacks, such as prolonged periods, harsh reaction conditions, poor yields, and the use of hazardous and expensive catalysts. Therefore, developing a clean, high-yielding, and environmentally benign approach is still desirable. We wish to report a clean and efficient method for the synthesis of fused pyrimidine derivatives in excellent yields through one-pot condensation of aromatic aldehydes, 4-hydroxy coumarin, and urea using resorcin[4]arene sulphonic acid as catalysts under solvent-free condition. The reaction is depicted in Scheme 1.



Scheme 1. Synthesis of Fused Pyrimidine Derivatives

In our continuing research, attention to exploring new and suitable synthetic protocols for the formation of bioactive heterocyclic derivatives, we report, herein, an alternative protocol for the synthesis of fused pyrimidine derivatives in the presence of resorcin[4]arene tetrasulfonic acid under in solvent-free medium. Resorcin[4]arene sulfonic acid has been bonded as a superb and recyclable organo-catalyst for synthesizing organic compounds [18-19]. Solvent-free conditions, as well as aqueous reaction media, nontoxicity, excellent yields, and especially ease of catalyst recovery, make this procedure valuable and environmentally benign in synthetic chemistry. This protocol involves an environment-friendly and cost-effective methodology. In addition, products from reactions catalyzed by non-metallic organic compounds are required by pharmaceutical and cosmetic industries. Due to this purpose, an organo-catalyst is a greener alternative for bioactive heterocyclic compound synthesis.

Calixarenes, macrocycles formed from condensation resorcinol with formaldehyde in an acid medium, have been widely used as ligands in organometallic catalysis. Nevertheless, their roles as organocatalytics are still poorly investigated.

2. Experimental

2.1. Materials and Chemicals

All reagents were purchased from Merck and Loba and used without further purification. Melting points were measured in open capillary and are uncorrected. IR spectra and 1H NMR analyses characterized the products. IR spectra were recorded on the Perkin–Elmer FT-IR-1710 instrument. Using TMS as an internal standard, 1H NMR was recorded on Bruker AC-200 MHz, BrukerMSL-300 MHz and Bruker DRX-500 MHz instruments.

2.2. Preparation of catalyst

The general method for synthesis of resorcin[4]arene is given in our previous study [18]. In a 100 mL two-necked round bottom flask equipped with a reflux condenser and dropping funnel, 11.0 g (0.1mol) of resorcinol and 12.6 mL (0.1mol) of 35% of acetaldehyde were placed. The mixture was stirred for 15 minutes at 10^0 C. Concentrated hydrochloric acid was carefully added to the above reaction mixture with the help of a dropping funnel. The precipitate was rapidly formed. The reaction mixture was stirred at 75°C for 1 hour, cooled in an ice bath, filtered, and washed with water. Recrystallize from ethanol: water (30:70) to obtain yellow-colored crystals of resorcin[4]arene.

The sulphonation of resorcin[4]arene was synthesized using a method described in the literature [19]. Resorcin[4]arene 1 gm was mixed with concentrated sulphuric acid, and the solution was heated at 70°C for 3 hrs. An aliquot was withdrawn from the reaction mixture and then poured into ice water to determine the progress of the reaction. The reaction was completed when no water-insoluble material was detected in the aliquot. After completion of the reaction, the reaction mixture precipitate was collected by filtration. Dissolve the residue in 5 mL of water. Finally, sulfonated resorcin[4]arene was obtained after evaporation of water (Yield 68%).

2.3. General Procedure for the Synthesis of Fused pyrimidine

The mixture containing the aldehyde (1.0 mmol), 4-hydroxy coumarin (1.0 mmol), urea (1.3 mmol), and resorcin[4]arene sulphonic acid (6 mol %) was heated at 80°C under solvent-free conditions for the appropriate time to complete the reaction check using TLC. After completion, the reaction mixture was cooled to room temperature, poured into crushed ice (20 g), and stirred for 2-5 min. The resultant product was collected by filtration under suction, washed with ice-cold water (4 mL), and recrystallized from hot ethanol to afford the pure product.

2.4. Selected Spectroscopic Data

4- phenyl -1,2,3,4 –tetrahydro[4,3-d]pyrimidine -2,5dione (1):
Yeild: 90%; Mp-162^{o}C;
IR (KBr)/cm^{-1}: 2924, 2727, 2360, 1654, 1459, 1379, 1303, 1154, 1075, 964, 722.
^{1}H NMR (300 MHz, DMSO-6): δ 6.34 (s, 1H), 7.16-7.59 (m, A9H), 7.89 (s, 1NH), 7.9 (s, 1NH).
^{13}CNMR (300 MHz, DMSO-d6): δ 38.83, 103.63, 115.59, 118.56, 123.82, 126.49, 127.75, 131.34, 140.73, 152.15, 164.56, 166.12.

4-(2 chloro phenyl)-1,2,3,4 –tetrahydro[4,3-d]pyrimidine -2,5-dione (2):
Yield: 90%; Mp-206-208^{o}C;
IR(KBr/cm^{-1}): 3513, 3402, 3300, 304, 1682, 1607, 1159, 1219, 1060, 757, 652, 53,493,453.
^{1}H NMR (300 MHz, DMSO-d6): δ 6.14 (s, 1H), 7.1-7.53 (m, 8H), 7.84 (s, 1NH), 7.86 (s, 1NH).
^{13}CNMR (300 MHz, DMSO- d6): δ 39.29, 103.63, 115.80,118.45, 123.37, 123.79, 129.31, 130.17, 131.43, 132.79, 139.38, 152.25, 163.38, 165.53.

4-(2 Hydroxy phenyl)-2 thioxo-1,2,3,4 –tetrahydro[4,3-d]pyrimidine -2,5dione (3):
Yield: 84%; Mp-168-170^{o}C;
IR (KBr/cm^{-1}): 3415, 3071, 2362, 1752, 1606, 1488, 1449, 1389, 1343, 1241, 1271, 1039, 940, 865, 752, 465.
^{1}H NMR (300 MHz, DMSO-d6): δ 3.3 (s, 1H, OH), 6.89-7.85 (m, 8H), 8.32 (s, 1H), 10.67 (s, 1H).
^{13}CNMR (300 MHz, DMSO-d6): δ 39.70, 116.23, 117.00, 118.45, 119.34, 123.57, 124.91, 128.97, 129.79, 130.89, 130.89, 133.32, 135.31, 142.83, 152.84, 158.11, 158.63, 191.91.

4-(3,4 dimethoxy phenyl)-1,2,3,4 –tetrahydro[4,3-d]pyrimidine -2,5dione (4):
Yield: 90%; Mp-270-272^{o}C;
IR (KBr/cm^{-1}): 2938, 2835, 2728, 2611, 2363, 1699, 1617, 1506, 1453, 1346, 1244, 1187, 1126, 1010, 907, 763, 506, 452.
^{1}H NMR (300 MHz, DMSO d6): δ 3.54 (s, 3H), 3.69 (s, 3H), 6.25 (s, 1H), 6.64-7.86 (m, 7H), 7.88 (s, 1H), 7.89 (s, 1NH).
^{13}CNMR (300 MHz, DMSO-d6): δ 39.09, 55.55, 104.26, 111.30, 111.54, 115.88, 118.85, 123.59, 123.90, 131.68, 132.63, 147.00, 148.35, 152.23, 164.68, 165.55.

4- phenyl -2 thioxo-1,2,3,4 –tetrahydro[4,3-d]pyrimidine -2,5dione (5):
Yield: 85%; Mp-188-190^{o}C;
IR (KBr/cm^{-1}): 2923, 2854, 1656, 1463, 1377, 1303, 1155, 970, 727.
^{1}HNMR (300 MHz, DMSO-d6): δ 6.36 (s, 1H), 7.17-7.60 (m, 9H), 7.88 (s, 1NH), 7.91 (s, 1NH).

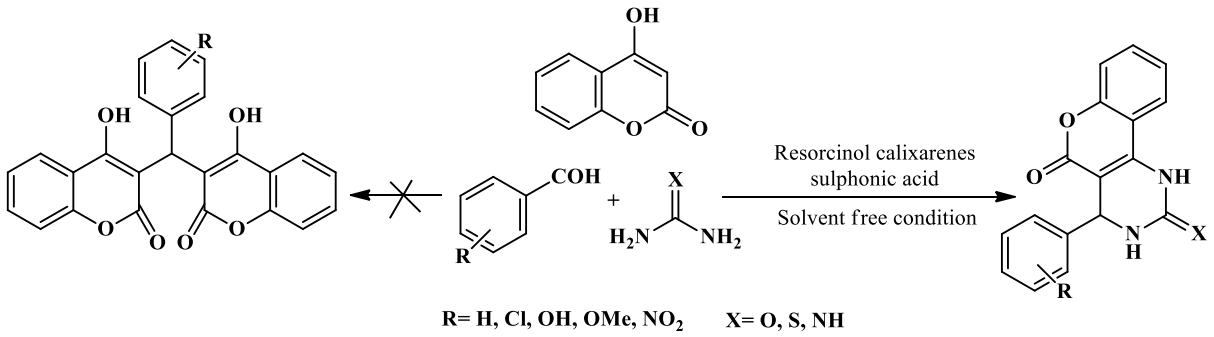
3. Results and Discussion

The fused pyrimidine was obtained in excellent yields within a shorter reaction time through the one-pot condensation of aromatic aldehydes (1mmol), 4-hydroxy coumarin (1mmol), and urea (1.2 mmol) using resorcin[4]arene sulphonic acid (6 mol%) as catalysts in a solvent-free condition. The results are summarised in Table 3.

To investigate the reaction in detail, a model reaction was carried out by condensing aldehyde, 4-hydoxycoumarin and urea in various solvent and catalyst (10 mol%) such as I_2, H_2SO_4, H_3PO_4, $POCl_3$, P_2O_5, p-TSA, $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, SSA, K_2CO_3, KH_2PO_4, CH_3COONa, TBABr, CTAB, L-proline. The results showed that when resorcin[4]arene sulphonic acid was used as a catalyst, its action was more effective than $H_3PW_{12}O_{40}$, p-TSA, L-proline, and no side product using this catalyst. In case entries 2, 3, 4, and 6, the biscoumarin with 70%, 63%, 80%, and 85% yields was obtained instead of the desired product. It was found that this three-component reaction has not yet been reported with guanidine. Hence, further reaction conditions have been explored with guanidine in the place of urea or thiourea. Surprisingly, the reaction could not occur with guanidine to construct fused pyrimidine; it could only obtain biscoumarin as a product. The reaction results are depicted in Table 1, and the reaction pathway is presented in Scheme 2.

Table 1. Optimization of the catalyst (10 mol%) for synthesizing fused pyrimidine one pot condensation between 4-hydroxy coumarin, benzaldehyde, and urea.

Entry	Catalyst	Solvent	Yield (%) Biscoumarin	Yield (%) Fused Pyrimidine
1	p-TSA	Solvent free condition	-	60
2	H_2SO_4	Ethanol	70	-
3	H_3PO_4	Ethanol	63	-
4	P_2O_5	Ethanol	80	-
5	SSA	Solvent free condition	-	45
6	I_2	Acetonitrile	85	-
7	$H_3PW_{12}O_{40}$,	Solvent free condition	-	80
8	$H_3PMo_{12}O_{40}$	Solvent free condition	-	65
9	$H_3PW_{12}O_{40}$+ $H_3PMo_{12}O_{40}$	Solvent free condition	-	78
10	PEG	Solvent free condition	-	43
11	Resorcin[4]arene Sulphonic acid	Solvent free condition	-	85
12	Resorcin[4]arene Sulphonic acid	water		65
13	Resorcin[4]arene Sulphonic acid	Water: ethanol (70 :30)	-	80
14	L-proline	water	-	67
15	K_2CO_3	Ethanol	80	-
16	TBABr	water	-	-
17	CH_3COONa	Methanol	87	-

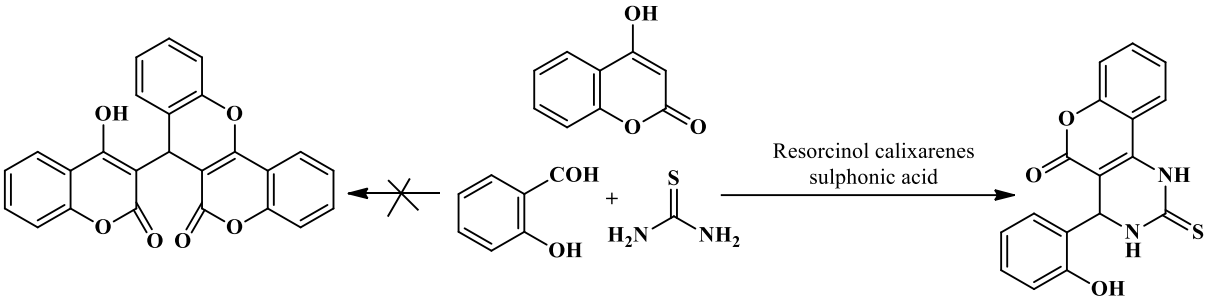


Scheme 2. Reaction pathway

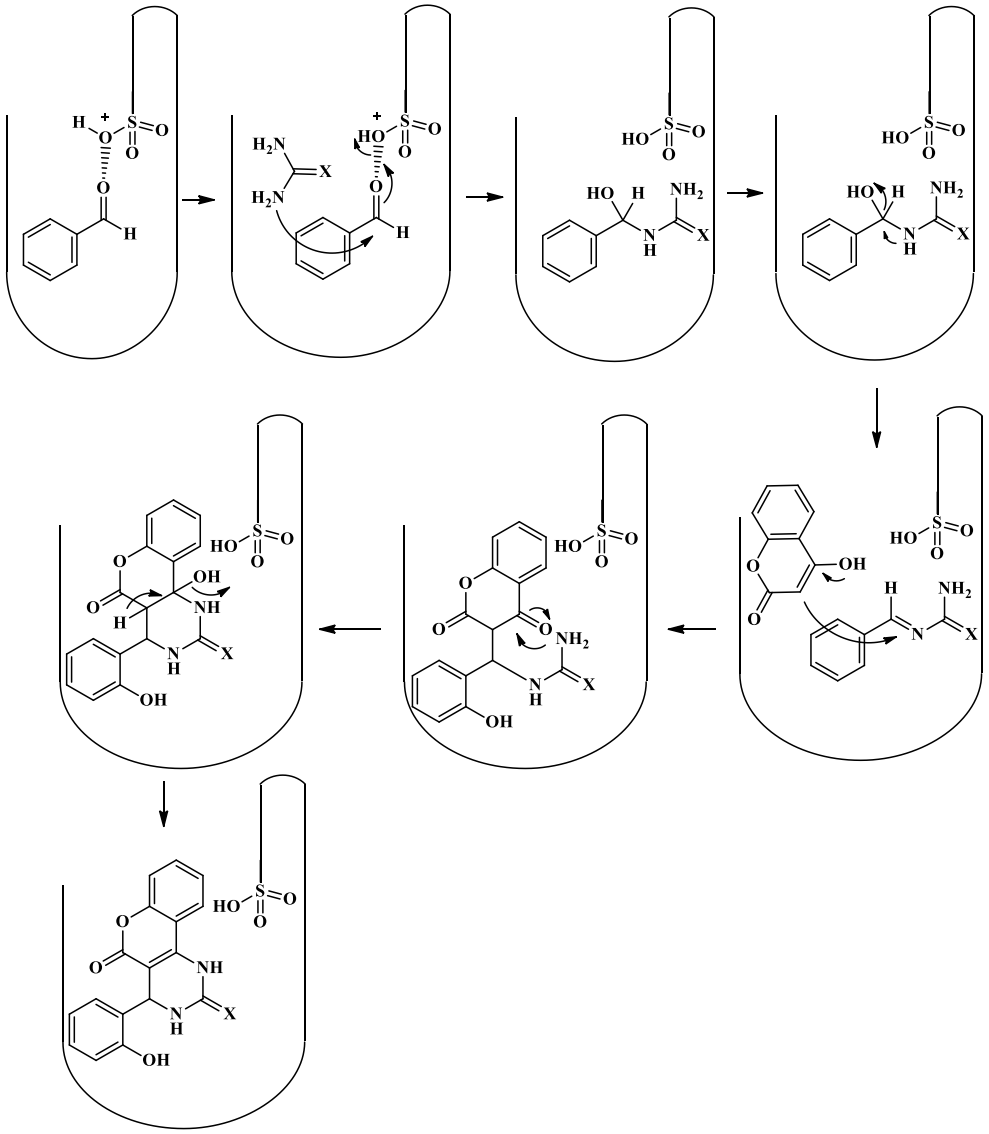
We have studied the effect of the catalyst concentration (resorcin[4]arene sulphonic acid) in an aqueous reaction medium. It was observed that 6 mol% of the catalyst was the optimum quantity to get the desired product with an excellent yield. The results are depicted in Table 2. Different aldehydes containing electron-withdrawing, electron-releasing substituents, and urea/thiourea were used for the universal applicability of the method for synthesizing fused pyrimidine. It was found that in all cases, the yields were excellent. In the present study, when resorcin[4]arene sulphonic acid catalyst was used as a catalyst in the reaction in an aqueous reaction medium, the exclusive product obtained was fused pyrimidine. We checked the selectivity of this reaction by using this catalyst with 2-hydroxy benzaldehydes, and then we got the desired product, not the chromone as a product (Scheme 3).

Table 2. Optimization of the amount of resorcin[4]arene sulphonic acid using solvent-free conditions at 80 °C.

Mmol % catalysts	Time (hr)	Yield (%)
4	1 hr, 30 min	80
6	1 hr,10 min	90
8	1 hr	87
10	1hr	85



Scheme 3. Reaction pathway



Scheme 4. The proposed mechanism for the synthesis of fused pyrimidine derivatives

In connection with our ongoing work on synthesizing heterocyclic compounds with reusable catalysts, we report a facile procedure for the preparation of fused pyrimidine with resorcin[4]arene sulphonic acid as a nontoxic, inexpensive organocatalyst. Aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly in all cases. They gave the products good yields by designing and synthesizing more selective catalysts for developing multi-component reactions [20-21]. We synthesized fused pyrimidine derivatives in a single pot using a resorcin[4]arene tetrasulfonic acid as a catalyst. Initially, enamine is formed from aldehydes and urea, which react in situ with 4-hydroxy coumarins in the presence of this catalyst to produce fused pyrimidine derivatives, as illustrated in Scheme 4.

1H NMR and 13C NMR further proved the Absolute configuration. In the case of fused pyrimidine derivative, there are two -NH groups and should give a sharp singlet at about 6 to 8 ppm in 1H NMR is the prediction of fused pyrimidine. However, in 1H NMR spectra of Biscoumarin and chromone compounds -NH peaks are absent, indicating that there are Fused pyrimidine derivatives.

Table 3. Resorcin[4]arene sulphonic acid-catalyzed one-pot condensation between 4-hydroxy coumarin, aldehydes, and urea at 6 mol%.

Entry	R	X	Time (M.W.) min	M.P ^{0}C	Yield %
1	H	O	1 hr 10	162	90
2	2-Cl	O	1 hr 20 min	206-208	90
3	2-OH	S	1 hr 30	168-170	84
4	3,4 Dimethoxy	O	1hr ,30 min	270-272	90
5	H	S	1.5 hr	188-190	85

We have also studied the effect of catalyst concentration (resorcin[4]arene sulphonic acid) in solvent-free conditions. It was observed that 6 mol% of the catalyst was the optimum quantity to get the desired product with an excellent yield. The results are depicted in Table 3. Different aldehydes containing electron-withdrawing, electron-releasing substituents, and 4-hydroxy coumarin were used for universal applicability in the presence of urea /thiourea, the method for the synthesis of fused pyrimidine. It was found that in all cases, the yields were excellent.

4. Conclusion

Resorcin[4]arene sulphonic acid has emerged as a promising organocatalyst for synthesizing fused pyrimidine derivatives, opening up new avenues for developing diverse molecules with potential applications in pharmaceuticals, material science, and beyond. This research explores the importance of innovative catalytic systems in advancing the field of organic synthesis. It sets the stage for further exploration of resorcin[4]arene sulphonic acid and related organocatalysts to pursue efficient and sustainable chemical transformation.

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