

Polymer supported sulphanilic acid: A highly efficient and recyclable green heterogeneous catalyst for the construction of 4,5-dihydropyrano[3,2-c]chromenes under solvent-free conditions

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Abstract. Polystyrene divinylbenzene supported sulphanilic acid was prepared, characterized and tested as an acidic catalyst in multicomponent organic synthesis. This is the first report focusing on the development of one-pot solvent-free synthesis of 4,5-dihydropyrano [3,2-c]chromenes under acidic conditions. It proved to be a versatile catalyst for microwave-assisted synthesis of 4,5-dihydropyrano[3,2-c]chromenes. This methodology is mild, high yielding, green and the catalyst could be easily recycled for several times.

Keywords. Heterogeneous catalyst; microwave; chromenes; solvent free; multi-component.

1. Introduction

The development of multi-component reactions (MCRs) designed to produce multifaceted biologically active compounds. It has become an important area of research in organic and medicinal chemistry.^{1–4} Dihydropyrano [3,2-c]chromenes and their derivatives are of considerable interest as they possess a broad spectrum of biological and pharmaceutical properties⁵ such as antidyslipidemic,⁶ anticancer,⁷ antimalarial,⁸ molluscicidal,⁹ and anti-inflammatory.¹⁰ These derivatives widely employed as pigments¹¹ and potential biodegradable agrochemicals.¹²

To date, a wide variety of Lewis base or basic catalysts have been efficiently promoted the synthesis of 4,5-dihydropyrano[3,2-c]chromenes such as nano ZnO,¹³ diammonium hydrogen phosphate,¹⁴ DBU,¹⁵ TBAB,¹⁶ KAl(SO₄)₂·12H₂O,¹⁷ TMGT,¹⁸ MgO,¹⁹ K₂CO₃,²⁰ pyridine,²¹ [bmim]OH,²² morpholine.²³ More recently, a one-pot, three component reaction of 4,5-dihydropyrano[3,2-c]chromenes promoted by DMAP²⁴ was also reported.

Recently, the use of heterogeneous catalyst has received considerable attention due to their operational advantages such as insolubility in organic solvent as well as in water. It can be easily recovered from reaction media and creates least hazard to environment.

However, certain limitations of heterogeneous catalysis are frequently encountered, such as lower efficiency or selectivity compared to that of homogeneous systems.^{25–27} To improve these properties, a variety of polymer-supported heterogeneous catalysts have been devised in recent years.^{28–30}

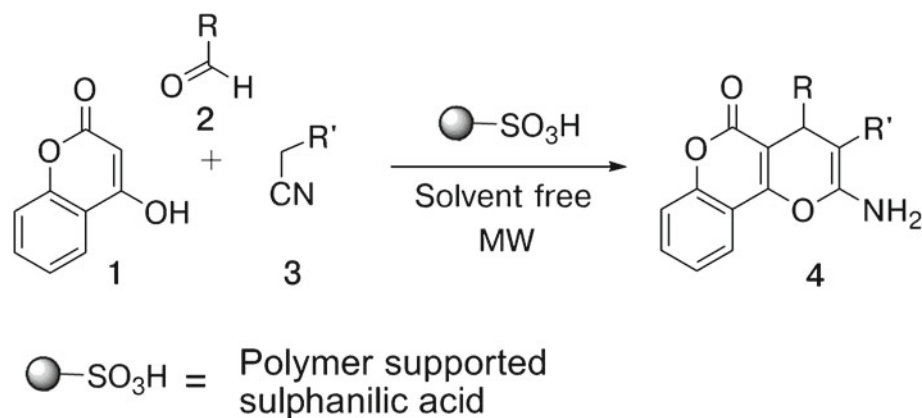
Despite of extensive studies on the reported reactions in the literature, to the best of our knowledge, there is no report focusing on the development of one-pot solvent-free synthesis of dihydropyrano [3,2-c]chromenes under acidic conditions using polymer supported acid catalyst. During the course of our studies on catalytic reactions^{31–36} in this paper, we disclose a simple method for surface modification and functionalization of cross-linked polystyrene-divinyl benzene with sulphanilic acid and used as a catalyst in microwave-assisted rapid, high yielding, and green synthetic protocol for the synthesis of pyran annulated heterocycles (scheme 1).

2. Experimental

2.1 General

All chemicals were of research grade and were used as obtained. The reactions were carried out by using 700 Watt CATA-R scientific microwave system. Melting points were measured in open capillaries and are uncorrected. TLC was performed on Silica Gel 60 F₂₅₄ pre-coated plates (Merck). IR spectra were recorded

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Scheme 1. General scheme for the synthesis of 4,5-dihydropyrano[3,2-c]chromenes.

on a Shimadzu FT-IR-S8401 spectrophotometer using KBr, mass spectra on a AB Applied Biosystems IMDS SciEx. API-2000 LC/MS/MS spectrometer, and elemental analysis on Perkin Elmer PE 2400 elemental analyzer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 MHz instrument with TMS as an internal standard.

2.2 Procedure for the preparation of chloromethylated polystyrene divinylbenzene (P2)

Polystyrene divinylbenzene beads **P1** (5 gm.) were allowed to swell in 30 ml chloro methyl methyl ether (CMME) for 2 h. To this, freshly prepared saturated solution of ZnCl_2 in THF (1.5 ml) was added and refluxed at 50°C for 6 h. After completion of reaction, the chloromethylated styrene-divinylbenzene beads were recovered by filtration and washed with THF, THF- H_2O (1:1 v/v), water and finally with methanol. It was then dried overnight *in vacuo* at room temperature. The resulting chloromethylated styrene-divinylbenzene copolymer beads were designated as **P2** and analysed for chlorine content by Stepnow method.³⁷

2.3 Procedure for polymer supported sulphanilic acid (P3)

P2 (5 gm) were dispersed in methanol (15 ml) and allowed to swell for 2 h. To the swollen bead, aqueous solution of sulphanilic acid (5 g, 4% w/v) was added and refluxed for 16 h in the presence of pyridine (3.5 ml) with continuous mechanical stirring. The content were cooled and kept aside for one week with occasional shaking. At the end of reaction, the pH of reaction mixture came down from the 8 to 4. The yield of the

modified thermosetting resin was 5.5 gm. Finally, the cross-linked polymer beads were filtered and washed with hot water followed by methanol and air dried under vacuum at room temperature for 24 h and it was designated as **P3**.

2.4 General procedure for the 4,5-dihydropyrano[3,2-c]chromenes

2.4a Microwave irradiation method (method A): A mixture of 4-hydroxycoumarin **1** (0.01 mol), Benzaldehyde **2** (0.01 mol) and Malanonitrile/Ethyl cyanoacetate **3** (0.012 mol) along with catalyst **P3** (5% w/w) was taken in 25 ml RBF, mixed well and irradiated in microwave oven at 280 W for appropriate time shown in table 2. The completion of the reaction was monitored by TLC. After completion, the flask was removed from the oven. The obtained product was extracted with chloroform; the insoluble polymer catalyst **P3** was filtrated off and the organic layer was dried *in vacuo*. The crude product was purified by recrystallization from ethanol. **P3** was washed twice with 5 ml aliquot of diethyl ether and was recycled for next four runs for the model reaction.

2.4b Conventional method (method B): A mixture of 4-hydroxycoumarin **1** (0.01 mol), Benzaldehyde **2** (0.01 mol), malanonitrile/ethyl cyanoacetate **3** (0.012 mol) and catalyst **P3** (5% w/w) in EtOH (5 ml) was stirred under reflux conditions for appropriate time. After completion of the reaction, the reaction mixture was filtered in hot water to remove the catalyst and the filtrate was allowed to cool at room temperature. The solid thus obtained was collected by filtration, washed with chilled aqueous ethanol and finally recrystallized from ethanol to give pure product.

2.5 Spectral data of the selected compounds

2.5a *3-Ethoxycarbonyl-2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene (4a)*: IR ν_{\max} (KBr): 3430, 3350, 3000, 2940, 2910, 1725, 1482, 1605, 1158 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.26 (t, 3H, $J = 7.2$ Hz), 4.15 (q, 2H, $J = 7.2$ Hz), 5.25 (s, 1H), 7.13–8.20 (m, 9H, Ar-H), 8.26 (2H, s); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 40.1, 60.1, 80.0, 100.0, 112.3, 117.0, 123.4, 124.8, 125.2, 128.6, 131.4, 135.0, 149.1, 153.3, 158.6, 159.8, 168.9, 175.0. Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4$: C, 69.41; H, 4.72; N, 3.85. Found C, 69.29; H, 4.85; N, 3.92. m/z (ESI): 364.2 $[\text{M} + \text{H}^+]$

2.5b *3-Carbonitrile-2-amino-5-oxo-4-(thiophen-2-yl)-4,5-dihydropyrano[3,2-c]chromene (4m)*: IR ν_{\max} (KBr): 3410, 3340, 3010, 1700, 2210, 724 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 5.20 (s, 1H), 7.24–7.78 (m, 7H), 8.23 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 39.0, 61.0, 101.2, 112.1, 116.0, 117.5, 120.0, 124.6, 125.1, 125.2, 135.2, 140.1, 141.6, 154.3, 154.9, 155.5, 167.9. Anal. Calcd for $\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$: C, 63.34; H, 3.13; N, 8.69. Found C, 63.45; H, 3.02; N, 8.52. m/z (ESI): 323.4 $[\text{M} + \text{H}^+]$.

3. Results and discussion

The polymer supported sulphanilic acid **P3** was prepared in two steps. As shown in scheme 2, the beads of polystyrene (**P1**, 4% divinyl benzene, 50 mesh) were treated with chloromethylmethylether (CMME) in the presence of ZnCl_2 in THF, to produce chloromethylated styrene divinyl benzene beads **P2**. The percentage chlorine content of **P2** was $\sim 20\%$ as analysed by Stepnow method.³⁷ Sulphanilic acid was then grafted on to **P2** in methanol under reflux in the presence of pyridine for 16 h to yield polystyrene divinyl benzene supported sulphanilic acid **P3**. The chemical modification of **P2** with sulphanilic acid has been confirmed by disappearance of sharp C–Cl peak (due to $-\text{CH}_2\text{Cl}$ groups) 670 cm^{-1} in IR analysis. Elemental analysis showed that the percentage of remaining chlorine to be less than 6.5%. The catalyst **P3** was characterized by IR spectroscopy, which revealed characteristic absorptions at 3200–3400

Table 1. Condition optimization on the basis of amount of **P3** as catalyst for the preparation of **4j**^a.

Entry	Catalyst (weight %)	Time (min.) ^b	Yield (%) ^c
1	0	8.0	68
2	2	3.0	88
3	5	2.0	94
4	10	2.5	92
5	15	3.0	92
6	20	3.5	90

^aReaction Conditions : 4-hydroxycoumarin (**1**, 1 mmol), benzaldehyde (**2**, 1 mmol) and malanonitrile (**3**, 1.2 mmol). Microwave power 280 W, solvent-free

^bReaction progress was monitored by TLC

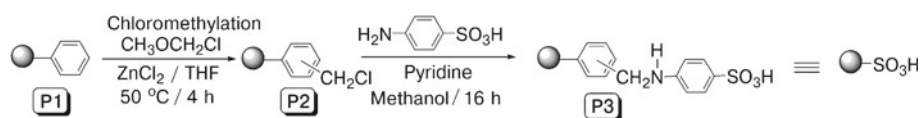
^cAll yields refer to isolated yield after crystallization

(OH and NH), 1320, 1150 cm^{-1} (SO_2), and by thermogravimetric analysis (TGA), which showed that **P3** is almost stable up to 150°C with the initial weight loss of only 0.58% due to loosely bound surface moisture or volatiles on the surface of catalyst. The weight loss in the range of 250°C to 350°C may due to the decomposition of sulphonic groups in to SO_2 and H_2O .³⁸ In order to confirm the presence of free sulphonic acid group after the functionalization of **P3** through amino group, the modified thermosetting resin was analysed to measure the degree of sulphonation using reported method³⁶ and was found to be 1.453 mmol per gram (free $-\text{SO}_3\text{H}$ content).

Initial study of **P3** as a catalyst was focused on the optimization of the model reaction of 4-hydroxycoumarin (**1**, 1 mmol), benzaldehyde (**2**, 1 mmol) and malanonitrile (**3**, 1.2 mmol) under solvent-free conditions (table 1) on the basis of amount of **P3**.

The control experiment (table 1, entry 1) without any added catalyst was completed in 8 min which took more time and produced lesser yield (68%) in comparison to the reactions performed using the reported catalyst.

The results revealed that only 5% of **P3** on the weight basis of 4-hydroxycoumarin is enough to lead the reaction to produce dihydropyrano [3,2-c]chromenes as high as in 94% of yield. Even the more amount of **P3** took relatively more time to produce almost same



Scheme 2. Synthetic pathway for the synthesis of polystyrene supported sulphanilic acid **P3**.

Table 2. Three-component reaction for the synthesis of 4,5-dihydropyrano [3,2-c]chromene derivatives promoted by **P3**.

Entry	R	R'	Product	Method A		Method B		Melting point	
				Time (s)	Yield ^c (%)	Time (h)	Yield ^c (%)	Observed	Reported
1	C ₆ H ₅	COOEt	4a	90	93	2.5	82	200	197–199 ³⁴
2	4-FC ₆ H ₄	COOEt	4b	60	94	1	80	230	–
3	3-FC ₆ H ₄	COOEt	4c	75	92	1.5	75	226	–
4	2-thiophenyl	COOEt	4d	60	94	2	85	220	–
5	2-furyl	COOEt	4e	120	94	1.5	82	210	–
6	3-Indolyl	COOEt	4f	180	92	2.5	75	208	–
7	4-MeOC ₆ H ₄	COOEt	4g	210	93	2	82	200	–
8	3,4,5-Tri(OMe)C ₆ H ₂	COOEt	4h	240	90	3	80	210	–
9	4-O ₂ NC ₆ H ₄	COOEt	4i	120	92	2	84	240	241–244 ²⁴
10	C ₆ H ₅	CN	4j	120	94	2	80	246	248 ¹³
11	4-FC ₆ H ₄	CN	4k	60	93	1	82	204	203 ¹³
12	3-FC ₆ H ₄	CN	4l	60	94	1.5	78	244	243–244 ³⁵
13	2-thiophenyl	CN	4m	60	94	1	87	226	228–229 ³⁶
14	2-furyl	CN	4n	90	93	1	85	216	215–217 ²⁰
15	3-Indolyl	CN	4o	150	92	2	80	214	215–217 ²⁰
16	4-MeOC ₆ H ₄	CN	4p	180	93	2.5	86	248	243–244 ³⁶
17	3,4,5-Tri(OMe)C ₆ H ₂	CN	4q	210	92	3	79	190	–
18	4-O ₂ NC ₆ H ₄	CN	4r	90	92	1.5	84	258	258–260 ³⁶

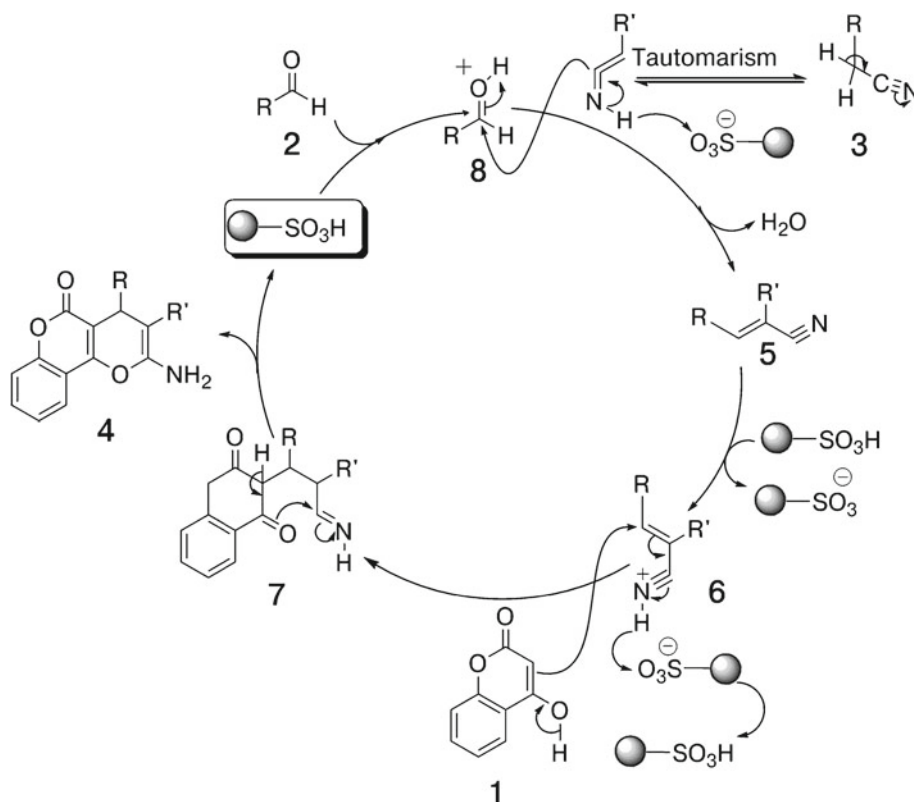
^aMethod A: Reaction carried out under solvent-free conditions at 280 W microwave irradiation

^bMethod B: Conventional method (reflux in methanol)

^cIsolated yield

yield. Therefore, 5% of **P3** was selected as the optimum amount of catalyst in the series of dihydropyrano [3,2-c]chromenes.

The scope and efficiency of this approach was explored for the synthesis of a wide variety of substituted 4,5-dihydropyrano[3,2-c]chromenes. The



Scheme 3. Plausible mechanism for the formation of 4,5-dihydropyrano[3,2-c]chromene.

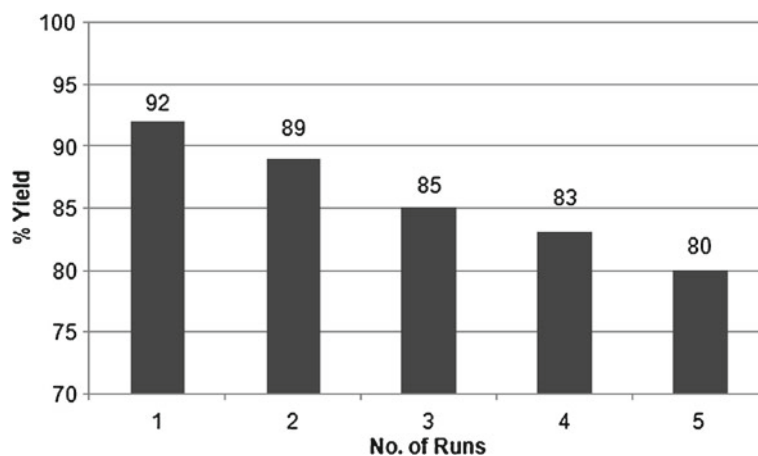


Figure 1. Recyclability study of catalyst **P3**.

obtained results are summarized in table 2. The reactions under microwave irradiation were completed within 1–4 min. The microwaves assisted **P3** catalysed method was found superior to the conventional one, as the reactions were high yielding, fast, and clean without any side products. The result of microwave irradiation and conventional heating for the synthesis of compounds (**4a–4r**) are compared in table 2.

All the aforementioned reactions delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both, electron-donating and electron-withdrawing substituents.

These three-component condensation reactions also proceeded with ethyl cyanoacetate (table 2, entries 1–9). It is observed that in entries 1–9 reaction times are longer. It may be due to the less activity of ethyl cyanoacetate than malononitrile. It is also observed that reaction was fast and also provided better yields using either aldehyde having electron withdrawing group such as NO_2 , F as compared to the aldehydes bearing electron releasing groups. In all the cases, obtained product was extracted with chloroform; the insoluble polymer catalyst **P3** was filtrated off and then remaining organic layer was dried *in vacuo*. The crude product was purified by recrystallization from ethanol. A plausible mechanism for these reactions is given in scheme 3.

In the synthesis of [3,2-*c*]chromenes, the first step is protonation of different aldehydes **2** by catalyst **P3** to form intermediate **8**. This intermediate **8** reacts with malononitrile/ethyl cyanoacetate to give Knoevenagel product with loss of H_2O . This Knoevenagel product **5** is further protonated by catalyst to yield intermediate **6**. Intermediate **6** and **1** interacting with each other through Michael addition to form intermediate **7**, which undergoes acid catalysed proton transfer as well as tautomerization to give the desired product 4 dihydropyrano [3,2-*c*]chromenes as shown in scheme 3.

It is noteworthy to mention that the catalyst is recyclable and could be reused without any significant loss in the activity. It could be recovered by simple filtration and washing with diethyl ether. The recycled catalyst was subjected to five more runs in the model reaction of **4j**. The results were almost consistent in yield after five runs (figure 1) within 10% of yield.

4. Conclusion

In conclusion, we have prepared and screened a new, efficient heterogeneous catalyst for the synthesis of dihydropyrano[3,2-*c*]chromenes. Only 5% of catalyst **P3** was found to be effectively catalyse the synthesis of chromenes in good to excellent yields. No column chromatography was sought for purification of products. High activity and easy handling make **P3** an ideal catalyst for this transformation. This work also opens up new avenues for other acid catalysed transformations using this catalyst and the research is ongoing in our laboratory.

Supporting information

^1H NMR and ^{13}C NMR spectra of compounds are available as supporting information in the journal website (www.ias.ac.in/chemsci).

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