

Perchloric acid modified-cellulose: a versatile, novel and biodegradable heterogeneous solid acid catalyst for singlepot synthesis of novel Bis-Pyran annulated heterocyclic scaffolds under solvent-free conditions

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Graphical abstract

An eco-friendly synthesis of novel bis-pyran annulated heterocyclic scaffolds (**4a-r**) and pyran annulated heterocyclic scaffolds (**4s-u**) using perchloric acid-modified cellulose (Cellulose-HClO₄) as a biodegradable and recyclable catalyst under solvent-free conditions.



Perchloric acid modified-cellulose: a versatile, novel and biodegradable heterogeneous solid acid catalyst for single-pot synthesis of novel Bis-Pyran annulated heterocyclic scaffolds under solvent-free conditions

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Abstract

One-pot multi-component, green, and highly efficient protocol has been developed for the synthesis of novel bis-pyran annulated heterocyclic scaffolds (**4a-r**) using cellulose perchloric acid (CPA) as an eco-friendly, biodegradable and recyclable catalyst in excellent yields under solvent-free conditions. Other remarkable features of this environmentally benign protocol are short reaction times, a wide range of functional group tolerance, use of inexpensive heterogeneous catalyst, high yield of products via a simple experimental and work-up procedure as compared to the conventional methods. The cellulose-HClO₄ (CPA) catalyst is characterized by using FTIR, powder XRD and SEM-EDX analyses. The stability of the catalyst was evaluated by TG/DTA characterization techniques. The catalyst can be recycled several times with a slight loss of its catalytic activity.

Keywords: Cellulose-HClO₄, bis-pyran annulated heterocycles, solvent-free conditions.

Introduction

2-amino-4H-Pyran annulated heterocyclic derivatives are excellent building blocks of naturally occurring products,¹ possessing numerous biological and pharmacological properties like anti-HIV, ² anti-tumor,³ anti-leishmanial,⁴ antioxidant,⁵ central nervous system (CNS) activities and effects,⁶ used for treatment of Alzheimer's disease⁷ and Schizophrenia disorder.⁸ Some 2-amino-4H-Pyran derivatives have been also utilized for the synthesis of laser dyes,⁹ photochromic materials,¹⁰ cosmetics, pigments,¹¹ agrochemicals.¹²They also serve as intermediates for the synthesis of organic compounds including pyridin-2-ones,¹³ pyrano[2]pyrimidines,¹⁴ lactones,¹⁵ imidoesters,¹⁵ pyranopyridine derivatives¹⁶ and polyazanaphthalenes.¹⁷

Due to the wide synthetic utility and potential applications of 2-amino-4H-pyran annulated heterocyclic scaffolds, various methods for their syntheses have been reported which include the use of homogeneous (piperidine,¹⁸ (S)-proline,¹⁹ K₃PO₄²⁰ DBU under microwave irradiation,¹⁶ amino functionalized ionic liquids²¹) as well as heterogeneous catalysts (chitosan,²² KSF,²³ cetyltrimethyl ammonium bromide,²⁴ Mg/La mixed metal oxides,²⁵ KF-Alumina,²⁶ heteropolyacid,²⁷). These methods, however, suffer from their own limitations, such as complicated multi-step reactions, low yield due to formation of side products, prolonged reaction times, use of harmful organic solvents, expensive catalysts and harsh reaction conditions with non-reusable catalysts.

Herein, we report synthesis of a series of 2-amino-4H-pyran annulated heterocyclic scaffolds using cellulose perchloric acid (CPA) under solvent-free conditions. The catalyst is novel, inexpensive and easily preparable. The catalyst is characterised by FTIR, powder XRD, scanning electron microscopy (SEM) and energy dispersion X-ray spectrometer (EDX) techniques. The stability of the catalyst was evaluated by thermogravimetric/differential thermal analyses (TG/DTA). It is pertinent to mention that cellulose is a biodegradable

polymer and serves as a unique support for the synthesis of solid acid catalysts including cellulose sulfuric acid which has been utilized in various organic transformations *viz*. synthesis of 1,4-dihydropyridines,²⁸ quinazolin-4(1H)-ones,²⁹ bis-chalcones³⁰ and bis-pyrazolines³⁰ etc.

Thus, in continuation of our interest in the development of heterogeneous, recyclable solid catalysts and novel methodologies³¹⁻³², we wish to report synthesis of a series of 2-amino-4H-pyran derivatives in excellent yields in very short time period via one-pot, three-component reaction of dialdehydes/substituted aldehydes, ethyl cyanoacetate/malononitrile and a variety of C-H activated acids in the presence of Cellulose-HClO₄ under solvent-free conditions (Scheme 1). The catalyst was recycled up to several runs.

Experimental

General information

Melting points of all synthesized compounds were taken in a Riechert Thermover instrument and are uncorrected. The IR spectra (KBr) were recorded on Perkin Elmer RXI spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DRX-300 and Bruker Avance II 400 spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO- d_6 /CDCl₃ as solvent. ESI-MS were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer having an ESI source. Elemental analyses (C, H and N) were conducted using the Elemental vario EL III elemental analyzer and their results were found to be in agreement with the calculated values. Chemicals were of commercial grade and used without further purification. The homogeneity of the compounds was checked by thin layer chromatography (TLC) on glass plates coated with silica gel G254 (E. Merck) using chloroform-methanol (3:1) mixture as mobile phase and visualized using iodine vapors. Xray diffractograms (XRD) of the catalyst were recorded in the 20 range of 10-70° with scan rate of 4°/min on a Rigaku Minifax X- ray diffractometer with Ni-filtered Cu K α radiation at

a wavelength of 1.54060° A. The SEM-EDX characterization of the catalyst was performed on a JEOL JSM-6510 scanning electron microscope equipped with energy dispersive X-ray spectrometer operating at 20 kV. TG/DTA was obtained with DTG-60H, with a heating rate of 20 $^{\circ}$ C /min from 0 to 500 $^{\circ}$ C under N₂ atmosphere.

Preparation of cellulose perchloric acid (CPA)

Cellulose-HClO₄ was prepared by the drop wise addition of perchloric acid (1.0 g, 10 mmol) to a magnetically stirred mixture of cellulose (5.0 g) in n-hexane (20 mL) at 0 °C during 2 h. After complete addition, the mixture was stirred for another 2 h. The mixture was filtered, washed with acetone (30 mL) and dried at room temperature to afford cellulose-HClO₄ as white powder (5.25 g).

Back titration analysis of Cellulose-HClO₄

NaOH solution (20 mL, 0.1 N) was added to the Cellulose-HClO₄ (100 mg) in an Erlenmeyer flask. This solution was stirred for 10 min. Excess amount of base was neutralized by addition of HCl solution (1 N) to the equivalence point of titration. NaOH solution (20 mL, 0.1 N) when added to cellulose (100 mg) without HClO₄ and subjected to back titration under similar condition, no change in the strength of NaOH was observed. This ruled out the possible reaction of NaOH with cellulosic-OH groups.

General procedure for the synthesis of 2-amino-4H-pyran annulated heterocyclic scaffolds (4a-u) under solvent-free conditions

A mixture of terephthaldehyde/isophthalaldehyde/substituted aldehydes (**1a-e**) (1.00 mmol), ethyl cyanoacetate/malononitrile (**2a-b**) (2.00/1.00 mmol), C-H activated acids (**3**) (2.00/1.00 mmol) and CPA (0.08 g) were mixed in a 25 mL round bottom flask and heated for the specific period of time at 70°C (Table 4, Table 5, Table 6 and Table 7). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and added EtOAc (5 mL) to it. The catalyst in the form of solid was filtered off from the reaction

mixture, washed with EtOAc (2 mL x 2), dried in oven at 70 °C and reused for further catalytic cycles. The filtrate was concentrated under reduced pressure to afford the products (4a-u). The pure products were obtained after recrystallization from ethanol (spectral data in Supporting Information).

Results and Discussion

Preparation and Characterization of Cellulose-HClO₄

The catalyst was prepared by adding perchloric acid to stirred solution of cellulose in nhexane. The number of H^+ sites on Cellulose-HClO₄ was determined by back titration and found as 1 meq/g.

The FT-IR spectrum of the catalyst exhibited a broad peak for OH absorption band at 3440 cm⁻¹. The peaks at 1158-1055 and 904 cm⁻¹ represented C-O stretching, C-C skeletal vibrations, and C₁-H ring stretching of the glucose unit, respectively.³³ The bands at 1158 and 1111 cm⁻¹ attributed to the asymmetric stretching whereas bands at 1055, 904 and 623, 551 cm⁻¹ were due to the symmetric stretching and rocking vibrations of HClO₄ (Fig. 1).³⁴



Fig. 1 FT-IR spectra of (a) Cellulose and (b) Cellulose-HClO₄.

The powder XRD pattern (Fig 2) of the matrix showed characteristic diffraction peaks for cellulose moiety at 16.5, 22.5 and 34° .³⁵



Fig. 2 Powder XRD of (a) Cellulose, (b) fresh Cellulose-HClO₄ and (c) Cellulose-HClO₄

after eight run.

The SEM micrographs (Fig. 3) were used to see surface morphology of CPA and

revealed a homogeneous fibrous surface.



Fig. 3 SEM images (a, b) of fresh catalyst (Cellulose-HClO₄) at different magnifications.

EDX analysis (Fig. 4) confirmed the presence of C, O and Cl elements in the synthesised CPA.



Fig. 4 EDX analysis of Cellulose-HClO₄.

To assess the thermal stability of Cellulose-HClO₄ (CPA), TG/DTA experiments were carried out and the thermograms are illustrated in (Figure 5). For TG/DTA analyses the sample was heated up to 500 °C at a constant rate of 20 °C /min in the nitrogen atmosphere. The weight losses found from TGA measurements agreed fairly well with those expected for the decomposition of cellulose perchloric acid to cellulose and perchloric acid group. As shown in Fig. 5 (a) the TG curve seems to indicate two-stage decomposition with a weight loss of 52.56 % between 77.70 °C and 147.79 °C which can be attributed to the evaporation of surface-physisorbed water. Another weight loss of 38.159 % between 367.38-417.31 °C can be due to the decomposition of the loaded perchloric acid along with cellulose polymer. Further evidence for the loss of physisorbed water and loaded perchloric acid on cellulose was provided by DTA measurement (Fig. 5 b).







Fig. 5 (b) DT Analysis of Cellulose-HClO₄

Catalytic activity of Cellulose-HClO₄

The catalytic activity of Cellulose-HClO₄ (CPA) was explored by facile synthesis of highly functionalized bis-pyran annulated heterocyclic scaffolds. In order to optimize reaction conditions, the reaction was studied by employing different solvents and solvent-free conditions at altered temperature with the expectation to maximize product yield in short reaction time (Table 1). For this purpose, condensation reaction between terephthaldehyde (1a) (1.00 mmol), ethyl cyanoacetate (2a) (2.00 mmol) and 4-hydroxycoumarin (3a) (2.00 mmol) was selected as a model reaction for the synthesis of compound 4a and the results are summarized in Table 1. It was observed that when the model reaction was carried out in ethanol in the absence of any catalyst under reflux condition, trace amount of the product was obtained after 21 hours (Table 1, entry 1), and indicated need of a catalyst. Then, the reaction was conducted in the presence of Cellulose-HClO₄ under the same conditions as above and yielded product (63%) in 4.8 hours. In acetic acid the reaction completed comparatively in lesser time but addition of water to obtain the product yielded a mixture of products whereas in other polar protic solvents such as methanol, iso-propanol, less yield of the desired product (4a) was obtained after longer time period (Table 1, entries 3–5). In aprotic solvents such as acetonitrile, chloroform, dichloromethane the product 4a was obtained in trace amount after longer time period whereas in dichloroethane 4a was obtained in low yield (Table 1, entries 6-9). Solvents such as water, THF and dioxane again didn't give satisfactory results (Table 1 entries 10-12). In environmentally benign solvents such as PEG-200, PEG-400, PEG-600, ethylene glycol, glycerol, the reaction again didn't yield fruitful results in terms of time and yield of the product (entries 13-17). However, the reaction performance was drastically enhanced under solvent-free conditions when the temperature was increased from 25 °C to 50 °C and then 70 °C and gave product 4a in excellent yield (98%) within few min (4 min) (Table 1, entries 18-20). Therefore, 70 °C was chosen as the optimum temperature in further

investigations. Further, increase in temperature to 80 °C did not show any significant enhancement in the yield of the desired product. Thus, our study revealed that solvent-free condition is the best condition for cellulose-HClO₄ catalysed formation of bis-pyran annulated heterocyclic scaffolds (Scheme 1) and dihydropyrano[c]chromene scaffolds in terms of enhanced yield of the products and reduced reaction time. The highest catalytic activity under solvent-free conditions may be due to the good dispersion of active reagent sites which facilitates better contact between reactant molecules and catalyst.³⁶ Moreover, due to absence of any solvent (as medium), there is no dilution effect and the heat needed for energy of activation is directly available to the reactant molecules.

Table 1 Effect of various solvents versus the solvent-free on the model reaction.^a



Entry	Solvent	Temperature	perature Time (min) ^b	
1	Ethanol ^d	Reflux	1260	Trace
2	Ethanol	Reflux	288	63
3	Acetic acid	Reflux	120	49(mixture)
4	Methanol	Reflux	360	42
5	Iso-propanol	Reflux	444	45
6	Acetonitrile	Reflux	780	Trace
7	Chloroform	Reflux	600	Trace
8	Dichloromethane	Reflux	480	Trace
9	Dichloroethane	Reflux	294	48
10	Water	Reflux	1440	-
11	THF	Reflux	1440	-
12	Dioxane	Reflux	1440	-
13	PEG-200	Reflux	288	34
14	PEG-400	Reflux	264	39
15	PEG-600	Reflux	240	42
16	Ethylene glycol	Reflux	420	30
17	Glycerol	Reflux	318	32
18	Solvent-free	25 °C	108	15
19	Solvent-free	50 °C	19	79
20	Solvent-free	70 °C	4	98
21	Solvent-free	80 °C	4	98

^a Reaction conditions: terephthaldehyde (1a) (1.00 mmol), ethyl cyanoacetate (2a) (2.00 mmol) and 4-hydroxycoumarin (3a) (2.00 mmol), catalyst (0.08 g). ^b Reaction progress monitored by TLC. ^c Isolated yields. ^d no catalyst.



Scheme 1 Cellulose-HClO₄ catalyzed synthesis of bis-pyran annulated heterocyclic scaffolds

(4a-r).

A comparative study was also carried out using a variety of catalysts for obtaining the best yield of **4a** under solvent-free conditions at 70 °C. The order of reactivity of various catalysts was Cellulose-HClO₄ > Perchloric-SiO₂ > PEG-OSO₃H > Zn(L-proline)₂ > HClO₄ > Sulfuric acid-SiO₂ > P₂O₅/SiO₂ > NaHSO₄-SiO₂ > P₂O₅ > PTS > Xanthan-OSO₃H > Sulfamic acid-SiO₂ > Camphor-sulfonic acid > L-proline > Chlorosulfonic acid > Amberlite IRC 50 >

Sulfamic acid = Sulfanilic acid in terms of yield of the product (Table 2). Since HClO₄ is strongest acid among the other acids/acid catalysts, the reaction was also conducted in HClO₄ alone and surprisingly provided product **4a** in 77% yield only. The product yield however, increased to a greater extent (98%) when cellulose-HClO₄ was used as catalyst. The highest catalytic activity shown by cellulose-HClO₄ in comparison to HClO₄ may be due to greater surface area and fine dispersion of catalyst on the surface of cellulose.

Table 2 Comparison of catalytic activity of different catalysts on the model reaction.^a



Entry	Catalyst	Conc. of H^+	Time (min) ^b	Yield (%) ^c
1	Cellulose-HClO ₄	(1 meq/g)	4	98
2^{37}	Perchloric-SiO ₂	(1.2 meq/g)	31	86
3^{38}	PEG-OSO ₃ H	(0.8 meq/g)	28	83
4 ³⁹	Zn(L-proline) ₂	- (10 mol%)	45	78
5^{40}	Sulfuric acid-SiO ₂	(1.3 meq/g)	114	76
6^{31}	P ₂ O ₅ /SiO ₂	(0.08 g)	43	75
7^{41}	NaHSO ₄ -SiO ₂	(0.08 g)	96	71
8	P_2O_5	- (10 mol%)	132	69
9	PTS	- (10 mol%)	84	67
10^{42}	Xanthan-OSO ₃ H	(0.8 meq/g)	186	66
11^{43}	Sulfamic acid-SiO ₂	(0.9 meq/g)	228	61
12	Camphor-sulfonic acid	- (10 mol%)	78	60
13	L-proline	- (10 mol%)	126	57
14	Chlorosulfonic acid	- (10 mol%)	90	49
15	Amberlite IRC 50	- (10 mol%)	258	37
16	Sulfamic acid	- (10 mol%)	1440	Trace
17	Sulfanilic acid	- (10 mol%)	1440	Trace
18	HClO ₄	- (10 mol%)	21	77

^a Reaction conditions: terephthaldehyde (1a) (1.00 mmol), ethyl cyanoacetate (2a) (2.00 mmol) and 4-hydroxycoumarin (3a) (2.00 mmol), solvent-free conditions, T=70 $^{\circ}$ C. ^b Reaction progress monitored by TLC. ^c Isolated yields.

The effect of different amounts of perchloric acid on cellulose support was also investigated when synthesizing **4a**, by using 5 mmol, 10 mmol and 15 mmol of perchloric acid supported on cellulose (5 g) (Table 3). With 5 mmol Cellulose-HClO₄ (lower ratio) unsatisfactory result was obtained in terms of yield and time possibly due to less available H^+ sites of the catalyst (entry 1). With 15 mmol Cellulose-HClO₄ the reaction completed in shorter time period but yield was not satisfactory possibly due to formation of some side products (entry 3). However, the excellent yield of the product was obtained with 10 mmol Cellulose-HClO₄ (entry 2).

	$+ \underbrace{\begin{pmatrix} \mathbf{N} \\ \mathbf{CO}_2 \mathbf{Et} \\ 2\mathbf{a} \\ \end{bmatrix}}_{2\mathbf{a}} \underbrace{\begin{pmatrix} \mathbf{OH} \\ \mathbf{O} \\ \mathbf{O} \\ \mathbf{OH} \\ $	ellulose-HClO ₄ Solvent-free 70 °C	H ₂ N O O CO_2Et O O O Aa EtO_2C NH_2	
Entry	Cellulose-HClO ₄	Time (min) ^b	Yield (%) ^c	
1	5 mmol	12	72	
2	10 mmol	4	98	
3	15 mmol	4	86	

Table 3 Effect of acid loading on the support for the model reaction.³

^a Reaction conditions: terephthaldehyde (1a) (1.00 mmol), ethyl cyanoacetate (2a) (2.00 mmol) and 4-hydroxycoumarin (3a) (2.00 mmol), catalyst (0.08 g), solvent-free conditions, $T=70^{\circ}C$. ^b Reaction progress monitored by TLC. ^c Isolated yields.

Variation of the catalyst loading also had profound effect on the catalytic activity (Fig. 6). When the reaction was carried out using 0.02 g, 0.04 g and 0.06 g of the catalysts, the rate of reaction progressed steadily with lower to moderate yields. However, the best performance was observed with 0.08 g of CPA under solvent-free conditions at 70 °C. Further increase in the catalyst loading had no significant enhancement in the yield of the

desired product and the rate of condensation reaction. Mechanistically (Scheme 2) all the H^+ sites of the catalyst with optimum amount (0.08 g) are utilized for the activation of substrate. Therefore, the catalyst with amount greater than 0.08 g does not have effect on activation of substrate.



Fig.6 Effect of catalyst loading on the model reaction

The recyclability of the catalyst is an important norm for heterogeneous catalysis in order to satisfy the green chemistry criteria. The recyclability of the catalyst was examined using model reaction of terephthaldehyde (1a) (1.00 mmol), ethyl cyanoacetate (2a) (2.00 mmol) and 4-hydroxycoumarin (3a) (2.00 mmol) in presence of CPA as catalyst under solvent-free conditions (Fig. 7). After completion of the reaction, the catalyst was recovered by filtration, washed with EtOAc (2 mL x 2) and dried in oven at 70 °C. The recovered catalyst was then employed for further eight additional repetitive runs adopting the identical protocol. After eight runs the catalyst showed some decrease in the product yield (Fig. 7).



Fig. 7 Recycling data of Cellulose-HClO₄ for model reaction.

Similar patterns of Powder XRD (Fig. 2b) and SEM-EDX analyses (Fig. 8 a, b and Fig. 9) were observed for the recovered catalyst with some low intensity and extra peaks which may be due to the catalyst deactivation or some changes in the morphology of the catalyst after eight runs. This fact was also checked by measuring the concentration of the residual H^+ on the recovered catalyst through titration method and showed marginal loss of H^+ sites (0.85 meq/g).



Fig. 8 SEM images (a, b) of the recovered catalyst (Cellulose-HClO₄) at different

magnifications.

P				Element	Weight%	Atomic%
				СК ОК СК	49.13 48.29 2.58	56.99 42.02 1.00
0				Totals	100.00	
9	<u></u>			• • • • • •	1 1 1 1 1	· · · · · · · · ·
0 2 4	6	8	10	12	14 16	18
Full Scale 209 cts Cursor: 0.000						keV

Fig. 9 EDX analysis of the recovered Cellulose-HClO₄.

Encouraged by the remarkable results, we explored the scope and generality of this novel protocol by the reaction of terephthaldehyde/isophthalaldehyde (**1a-b**), ethyl cyanoacetate/malononitrile (**2a-b**) with and 4-hydroxycoumarin (**3a**) in presence of CPA as catalyst under solvent-free conditions. All the reactions proceeded smoothly and were completed within 4-7 min to afford the products (**4a-c**) in excellent yield (97-98%) (Table 4). By replacing 4-hydroxycoumarin with 4-hydroxy-6-methyl-2H-pyran-2-one (**3b**), all the reactions proceeded efficiently to produce the desired products (**4d-f**) in higher yields (95-96%) within a short time period using the same procedure (Table 4).

Table 4 Cellulose-HClO4 catalyzed synthesis of bis-dihydropyrano[c]chromene (4a-c) andbis-dihydropyrano[b]pyran (4d-f) scaffolds^a





^a Reaction conditions: terephthaldehyde/isophthalaldehyde, (**1a-b**, 1.00 mmol), alkyl nitrile (**2a-b**, 2.00 mmol), activated C–H-acids (**3a-b**) (2.00 mmol), catalyst (0.08 g), solvent-free conditions, T=70 $^{\circ}$ C. ^b Reaction progress monitored by TLC. ^c Isolated yields. ^d The products were confirmed by melting points and compared with reported literature.^{44,45}

To further explore scope of the reaction for construction of bis-pyran annulated heterocyclic scaffolds, the reaction was conducted with 1,3-dimethyl barbituric acid (3c) and indane-1,3-dione (3d) as C-H-activated acids by adopting the identical protocol. The reactions went on well affording the products (4g-i) and (4j-l) in very good yields (95-98%) in a short span of time (Table 5).

Table 5 Cellulose-HClO4 catalyzed synthesis of bis-tetrahydropyrano[d]pyrimidine (4g-i)and bis-dihydroindeno[b]pyran (4j-l) scaffolds^a





^a Reaction conditions: terephthaldehyde/isophthalaldehyde, (**1a-b**, 1.00 mmol), alkyl nitrile (**2a-b**, 2.00 mmol), activated C–H-acids (**3c-d**) (2.00 mmol), catalyst (0.08 g), solvent-free conditions, T=70°C. ^b Reaction progress monitored by TLC. ^c Isolated yields.

Extending the present study to other C–H-activated acids such as dimedone (**3e**) and 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3f**) the corresponding products (**4m-o**) and (**4p-r**) were isolated in excellent yields (94-96%) under the optimized reaction conditions (Table 6).

Table 6 Cellulose-HClO4 catalyzed synthesis of bis-dihydropyrano[c]pyrazole (4p-r) andbis-benzo[b]pyrans (4m-o) scaffolds^a





^a Reaction conditions: terephthaldehyde/isophthalaldehyde, (**1a-b**, 1.00 mmol), alkyl nitrile (**2a-b**, 2.00 mmol), activated C–H-acids (**3e-f**) (2.00 mmol), catalyst (0.08 g), solvent-free conditions, T=70 $^{\circ}$ C. ^b Reaction progress monitored by TLC. ^c Isolated yields. ^d The products were confirmed by melting points and compared with reported literature.^{46,47}

In addition, the reaction of 4-hydroxycoumarin (**3a**), malononitrile (**2a**) with substituted aldehydes (**1c-e**) were also investigated to obtained dihydropyrano[c]chromene scaffolds (**4s-u**) under similar reaction conditions with higher yields (95-98%) in shorter time period.



Table 7 Cellulose-HClO₄ catalyzed synthesis of dihydropyrano[c]chromene scaffolds^a (4s-u)

^a Reaction conditions: substituted aldehydes (**1c-e**, 1.00 mmol), alkyl nitrile (**2b**, 1.00 mmol,), activated C–H-acid (**3a**, 1.00 mmol), catalyst (0.08 g), solvent-free conditions, T=70°C. ^b Reaction progress monitored by TLC. ^c Isolated yields. ^d The products were confirmed by melting points and compared with reported literature.⁴⁴

The structure of compounds (**4a-u**) was deduced on the basis of their spectral analysis. The IR spectrum of the newly synthesised compound **4a** showed broad bands for NH₂ groups at 3198, 3321 and 3396 cm⁻¹ and a sharp strong band at 1710 cm⁻¹ for C=O of the ester group. Other strong and sharp bands at 1674 and 1603 cm⁻¹ were for carbonyl group of coumarin moiety and C=C (vinylamine) respectively. The proton nuclear magnetic resonance spectroscopy (¹H NMR) exhibited multiplets from δ 1.21-1.31 and δ 3.98-4.14 for

CH₃ and CH₂ groups of ethyl cyanoacetate moiety. Another singlet integrating for two protons at δ 4.44 was assigned to methine proton. The four NH₂ protons were discernible as singlets at δ 6.77. Four aromatic protons appeared as singlet at δ 7.16. Other aromatic protons appeared as a multiplet in the region δ 7.29-7.75. The ¹³C NMR spectrum showed signals at δ 13.94, 61.20 for CH_3 and CH_2 groups of ethyl cyanoacetate moiety whereas methine (C-4) and C-3 carbons appeared at δ 37.12 and 74.72 respectively. The aromatic carbons appeared in the range of δ 121.10-138.20 and signal at δ 161.21 was for C-2 carbon. Signals at δ 169.30 and 174.71 were for carbonyl carbons of ester and coumarin moiety respectively. Further confirmation for 4a was provided by the ESI mass spectrum, which showed the molecular ion peak as base peak at m/z 648.2 (M⁺+1). A plausible mechanism for the formation of bis-pyran annulated heterocyclic scaffolds is depicted in Scheme 2. The initial step of the catalytic cycle involved the *in situ* formation of bis-Knoevenagel condensation product (5a) by the reaction of dialdehyde (1a), ethyl cyanoacetate (2a) in the presence of CPA which was followed by Michael addition between the bis-Knoevenagel product (5a) and C-H-activated acid (3a), to give 6a followed by the intra-molecular cyclization of 6a yielded **4a**.



Scheme 2 Plausible mechanism for the synthesis of (4a).

Heterogeneity test

The leaching and heterogeneity of Cellulose-HClO₄ was measured by hot filtration test employing terephthaldehyde, ethyl cyanoacetate and 4-hydroxycoumarin in ethanol as a solvent and catalytic amount of Cellulose-HClO₄. The reaction was refluxed for 30 min after which the catalyst was filtered under hot conditions. The reaction was then continued under same conditions without catalyst for further 6 hours and it was observed that the reaction couldn't proceed further. Therefore, it can be concluded that the catalyst is heterogeneous in nature.

Conclusion

In conclusion, we have developed an eco-efficient and simple procedure for the expedient synthesis of novel bis-pyran annulated heterocyclic scaffolds using Cellulose-HClO₄ as an environmentally benign and heterogeneous biopolymer-based solid acid catalyst under solvent-free conditions. The novel catalyst was efficiently applicable to a wide variety of C-H activated acids, affording the corresponding bis-pyran annulated heterocyclic scaffolds in

excellent yields. The catalyst was easily recoverable and recycled for eight runs. These features will facilitate this procedure to find extensive applications in the field of organic synthesis.

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