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Article

An Efficient Synthesis of Novel Bis-Chalcones and Bis-Pyrazolines in the Presence of Cellulose Sulfuric Acid as Biodegradable Catalyst under Solvent-Free Conditions

Zeba N. Siddiqui and Tabassum Khan*

Department of Chemistry, Aligarh Muslim University, 202002 Aligarh, India

Uma aproximação altamente eficiente e prática para a síntese de novas bis-chalconas heterocíclicas e as pirazolinas correspondentes foi desenvolvida usando-se celulose sulfonada como um catalisador ambientalmente benigno, biodegradável e reutilizável em condições livres de solvente. O catalisador pode ser utilizado várias vezes sem perda significativa de sua atividade catalítica.

A highly efficient and practical approach for the synthesis of novel heterocyclic bis-chalcones and corresponding pyrazolines has been developed using cellulose sulfuric acid as environmentally benign, biodegradable and reusable catalyst under solvent-free conditions. The catalyst can be reused several times without significant loss of its catalytic activity.

Keywords: cellulose sulfuric acid, heterocyclic bis-chalcones, heterocyclic bis-pyrazolines, heterogeneous catalysis

Introduction

Chalcones (1,3-diaryl/heteroaryl-2-propene-1-ones), are important pharmacophores of various natural products.[1] The examples of approved therapeutic agents incorporating this molecular framework include 3-methoxy-4-hydroxyloncocarpin (NADH:ubiquinone oxidoreductase activity inhibitor), xanthohumol (antioxidant) and coumarin-chalcone (anticancer agents), respectively (Figure 1). Many functionalized derivatives are also used as antidiabetic, antitubulin, NO production inhibitor, peritoneal antiangiogenic, antiproliferative agents and probe to study protein-dye interactions.[2-6]

They are generally synthesized via Claisen-Schmidt condensation carried out in basic or acidic media under homogeneous conditions in the presence of various catalysts.[7-12] However, in spite of their potential utility, many of the reported methods suffer from certain drawbacks like refluxing in hazardous organic solvents for prolonged time, use of expensive and toxic catalysts, high temperature and low product yields, harsh reaction conditions with non-recyclable catalysts.

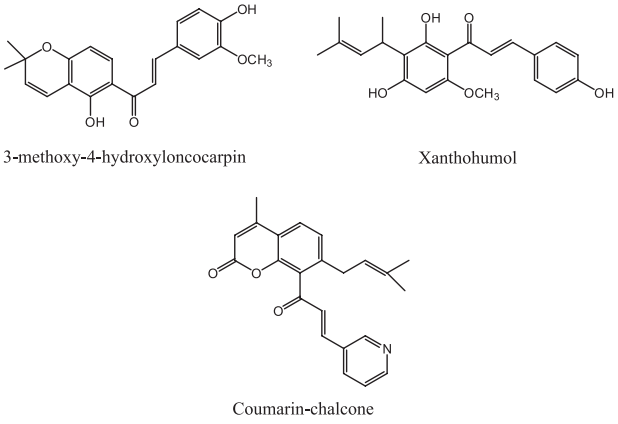


Figure 1. Biologically important chalcones.

Heterogeneous solid acid catalysts have received special attention as user-friendly catalysts due to environmental, economic and industrial aspects. Due to good dispersion of active reagent sites, associated selectivity and easier work-up procedures, various organic reactions are performed in the presence of heterogeneous catalysts and thus have advantages over the conventional solution phase reactions.[13] These catalysts are also advantageous over homogeneous catalysts as they can be recovered and reused several times to achieve very high turnover numbers, thereby making the process economically viable.[14] These days, science and

*e-mail: siddiqui_zeba@yahoo.co.in

technology is shifting emphasis on eco-friendly, natural product resources and reusable catalysts. In this regard, natural biopolymers are attractive candidates for solid supported catalysis.[15] Cellulose, one of the most abundant natural biopolymers in the world, has been widely studied during the past decades because it is both biodegradable and a renewable resource. It is an attractive alternative to conventional organic or inorganic supports in catalytic applications due to its unique properties.[16] It is extremely inert, inexpensive, and have high hydrothermal stability. Recently, cellulose sulfuric acid (CSA) has been employed for the synthesis of thiadiazolo benzimidazoles, pyrroles, 1,4-dihydropyridines, 2,3-dihydroquinazolin-4-ones and Ugi reaction.[17-21]

Thus, based on the above findings and in continuation of our interest in the development of efficient, economical and new methodologies,[22] we herein report, cellulose sulfuric acid (CSA) as a biodegradable and recyclable solid acid catalyst, for the synthesis of novel heterocyclic bis-chalcones and bis-pyrazolines under thermal solvent-free conditions in excellent yields.

The structure and morphology of the catalyst was established for the first time with the help of powder X-ray diffractograms (XRD), scanning electron microscopy (SEM) and energy dispersion X-ray spectrometer (EDX). The stability of the catalyst was evaluated by thermogravimetric/differential thermal analysis (TG/DTA) characterization techniques.

Experimental

Melting points of all synthesized compounds were taken in a Riechert Thermover instrument and are uncorrected. The Fourier transform infrared (FT-IR) spectra (KBr) were recorded on Perkin Elmer RXI spectrometer. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C 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/$CDCl_3$ as solvent. Electrospray ionization mass spectra (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. 3-Acetyl-4-hydroxycoumarin, 5-acetyl-1,3-dimethyl barbituric acid, 5-acetyl-barbituric acid and 5-acetyl-thiobarbituric acid,[23-25] were synthesized by reported procedures. Dehydroacetic acid was purchased from E. Merck (Merck, Darmstadt, Germany). Other 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 by iodine vapours. XRD of the catalyst were recorded in the 2θ range of 10-70° with scan rate of 4° min^{-1} on a Rigaku Minifax X-ray diffractometer with Ni-filtered Cu Kα radiation at a wavelength of 1.54060 Å. 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 °C min^{-1} from 0 to 500 °C under N_2 atmosphere.

Preparation of cellulose sulfuric acid

Cellulose sulfuric acid was prepared by the dropwise addition of chlorosulfonic acid (1.0 g, 9 mmol) to a magnetically stirred mixture of cellulose (5.0 g) in *n*-hexane (20 mL) at 0 °C during 2 h. HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred for another 2 h. Then the mixture was filtered, washed with 30 mL of acetonitrile and dried at room temperature to afford 5.25 g of cellulose sulfuric acid as a white powder. The number of H^+ sites on the cellulose-SO_3H, determined by back titration, was 0.50 meq g^{-1}.[26]

General procedure for the synthesis of bis-chalcones (**3a-e**) under solvent-free conditions

Terephthaldehyde **1** (1.00 mmol), 3-acetyl-4-hydroxycoumarin/dehydroacetic acid/5-acetyl-1,3-dimethylbarbituric acid/5-acetylbarbituric acid/5-acetylthiobarbituric acid (**2a-e**) (2.00 mmol) and CSA (0.06 g) were mixed thoroughly using a mortar and pestle, transferred to an open pyrex 100 mL beaker and heated at 70 °C for the given time (Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and added ethyl acetate (5 mL). The reaction mixture was filtered to remove the catalyst and concentrated to furnish pure products (**3a-e**).

2'*E*,2"*E*-3',3"-(1,4-Phenylene)bis(1-(4-hydroxy-1-benzopyran-2-one-3-yl))prop-2-en-1-one (**3a**)

Yellow powder; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1620 (C=C), 1668 (C=O), 1719 (C=O), 3106 (OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.07-7.15 (m, 8H, Ar-H), 7.41 (d, 2H, *J* 15.56 Hz, 2 H_a), 7.91 (d, 2H, *J* 15.68 Hz, 2 H_b), 7.56 (s, 4H, C_6H_4), 8.87 (s br, 2H, 2 OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 103.05 (2 C-3), 115.53 (2 C-10),

Table 1. Synthesis of bis-chalcones[a] (**3a**-**e**) and their derived bis-pyrazolines[b] (**5a**-**j**)

entry	Product	R	time[c] / min	Yield[d] / %
1	**3a**	–	3	98
2	**3b**	–	4	98
3	**3c**	–	6	96
4	**3d**	–	9	95
5	**3e**	–	9	95
6	**5a**	H	3	98
7	**5b**	Ph	3	97
8	**5c**	H	4	98
9	**5d**	Ph	4	97
10	**5e**	H	6	96
11	**5f**	Ph	6	95
12	**5g**	H	7	95
13	**5h**	Ph	6	96
14	**5i**	H	7	96
15	**5j**	Ph	8	95

[a]Reaction conditions: terephthaldehyde (**1**, 1.00 mmol); different cyclic active methyl compounds (**1a**-**e**, 2.00 mmol); CSA (0.06 g); solvent-free conditions; 70 °C; [b]reaction conditions: bis-chalcones (**3a**-**e**, 1.00 mmol); hydrazines (**4a**-**b**, 2.00 mmol); CSA (0.06 g); solvent-free conditions; 70 °C; [c]reaction progress monitored by TLC; [d]isolated yields.

122.16 (2 C-2'), 122.50, 125.52, 127.88, 130.73, 131.60, 135.57, 136.63 (Ar–C, C_6H_4–C), 153.51 (2 C-3'), 163.81 (2 C-2), 176.62 (2 C-4), 188.66 (2 C-1'); ESI-MS: *m/z* 507.0 ($M^+ + 1$); anal. calcd. for $C_{30}H_{18}O_8$: C, 71.21; H, 3.56; found: C, 70.81; H, 3.16.

2'*E*,2"*E*-3',3"-(1,4-Phenylene)bis(1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl))prop-2-en-1-one (**3b**)

Pale yellow solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1636 (C=C), 1695 (C=O), 1723 (C=O), 3106 (OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 6H, 2 CH3), 6.00 (s, 2H, 2 H_5), 7.72 (d, 2H, *J* 13.08 Hz, 2 H_a), 7.92 (s, 4H, C_6H_4,), 8.41 (d, 2H, *J* 16.08 Hz, 2 H_b); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.89 (2 CH3), 95.11 (2 C-3), 104.95 (2 C-5), 122.31 (2 C-2'), 127.01, 132.39 (C_6H_4–C), 153.29 (2 C-3'), 162.5 (2 C-6), 164.9 (2 C-2), 167.01 (2 C-1'), 185.35 (2 C-4); ESI-MS: *m/z* 435.1 ($M^+ + 1$); anal. calcd. for $C_{24}H_{18}O_8$: C, 66.42; H, 4.15; found: C, 66.03; H, 3.77.

2'*E*,2"*E*-3',3"-(1,4-Phenylene)bis(1-(1,3-dimethyl-2,4,6-pyrimidinetrione-5-yl))prop-2-en-1-one (**3c**)

Light yellow solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1620 (C=C), 1673 (C=O), 1725 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.33 (s, 12H, 4 N–CH_3), 7.77-7.92 (m, 4H, C_6H_4), 8.32 (d, 2H, *J* 14.72 Hz, 2 H_a), 8.47 (d, 2H, *J* 13.96 Hz, 2 H_b); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.81 (4 CH_3), 86.21 (2 C-5), 122.89 (2 C-2'), 133.94, 136.01 (C_6H_4–C), 154.14 (2 C-3'), 162.97 (2 C-2), 176.63 (2 C-4, C-6), 184.56 (2 C-1'); ESI-MS: *m/z* 495.3 ($M^+ + 1$); anal. calcd. for $C_{24}H_{22}N_4O_8$: C, 58.35; H, 4.45; N, 11.33; found: C, 58.74; H, 4.84; N, 11.73.

2'*E*,2"*E*-3',3"-(1,4-Phenylene)bis(1-(2,4,6-pyrimidinetrione-5-yl))prop-2-en-1-one (**3d**)

Yellow powder; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1628 (C=C), 1676 (C=O), 1700 (C=O), 3173 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.72 (d, 2H, *J* 15.52 Hz, 2 H_a), 7.75-7.93 (m, 4H, C_6H_4), 8.35 (d, 2H, *J* 15.04 Hz, 2 H_b), 10.00 (s, 4H, 4 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 90.40 (2 C-5), 122.03 (2 C-2'), 129.90, 135.59 (C_6H_4–C), 152.92 (2 C-3'), 163.98 (2 C-2), 177.35 (2 C-4, C-6), 185.01 (2 C-1'); ESI-MS: *m/z* 439.2 ($M^+ + 1$); anal. calcd. for $C_{20}H_{14}N_4O_8$: C, 54.84; H, 3.19; N, 12.78; found: C, 55.04; H, 3.39; N, 12.98.

2'*E*,2"*E*-3',3"-(1,4-Phenylene)bis(1-(2-mercapto-4,6-pyrimidinedione-5-yl))prop-2-en-1-one (**3e**)

Orange solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1151 (C=S), 1606 (C=C), 1665 (C=O), 1716 (C=O), 3105 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.55-8.14 (m, 8H, 4H, C_6H_4, 2 H_a and 2 H_b), 9.97 (s, 2H, 2 NH), 10.86 (s br, 2H, 2 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 88.43 (2 C-5), 123.13 (2 C-2'), 128.18, 132.37(C_6H_4–C), 153.12 (2 C-3'), 162.51 (2 C-2), 166.89 (2 C-4, C-6), 187.01 (2 C-1'); ESI-MS: *m/z* 471.2 ($M^+ + 1$); anal. calcd. for $C_{20}H_{14}N_4O_6$: C, 51.11; H, 2.89; N, 11.91; found: C, 50.81; H, 2.59; N, 11.61.

General procedure for the synthesis of bis-pyrazolines (**5a-j**) under solvent-free conditions

The compound **3a**-**e** (1.00 mmol) and hydrazines (hydrazine hydrate (2.00 mmol)/phenyl hydrazine (2.00 mmol)) and CSA (0.06 g) were mixed well and heated at 70 °C in a 100 mL beaker. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and added ethyl acetate (5 mL). The reaction mixture was filtered to remove the catalyst and concentrated to furnish pure products **5a-j**.

5',5"-(1,4-Phenylene)bis(3-(4-hydroxy-1-benzopyran-2-one-3-yl))pyrazoline (**5a**)

Light green solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1314 (C–N), 1612 (C=N), 1676 (C=O), 3201 (NH), 3257 (OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.41 (dd, 2H, *J* 18.68, 9.8 Hz, 2 Hd), 4.13 (dd, 2H, *J* 18.5, 9.9 Hz, 2 Hc), 4.90 (m, 2H, 2 He), 7.22-7.95 (m, 12H, 8 Ar–H and 4H C_6H_4), 8.24 (s, 2H, 2 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.85

(2 C-5'), 59.62 (2 C-4'), 95.48 (2 C-3), 113.18, 116.42, 119.55,120.78, 123.41, 125.23, 128.10, 131.07 (Ar–C, C_6H_4-C), 153.61 (2 C-3'), 170.18 (2 C-2), 180.41 (2 C-4); ESI-MS: *m/z* 535.1 (M^+ + 1); anal. calcd. for $C_{30}H_{22}N_4O_6$: C, 67.47; H, 4.12; N, 10.48; found: C, 67.37; H, 4.02; N, 10.38.

1',1″-Phenyl-5',5"-(1,4-phenylene)bis(3-(4-hydroxy-1-benzopyran-2-one-3-yl))pyrazoline (**5b**)

Dark yellow solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1326 (C–N), 1620 (C=N), 1708 (C=O), 3406 (OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.41 (dd, 2H, *J* 9.24, 5.8 Hz, 2 Hd), 4.22 (dd, 2H, *J* 18.50, 12.12 Hz, 2 Hc), 5.42 (m, 2H, 2 He), 6.72-8.02 (m, 22H, 18 Ar–H and 4H C_6H_4); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.02 (2 C-5'), 59.49 (2 C-4′), 99.19 (2 C-3), 111.49, 116.03, 116.49, 119.12, 121.11, 125.25, 126.59, 128.40, 131.07, 133.77, 136.28, 138.89 (Ar–C, C_6H_4–C), 149.93 (2 C-3'), 171.50 (2 C-2), 178.91 (2 C-4); ESI-MS: *m/z* 687.3 (M^+ + 1); anal. calcd. for $C_{42}H_{30}N_4O_6$: C, 73.53; H, 4.37; N, 8.16; found: C, 73.23; H, 4.07; N, 7.86.

5',5"-(1,4-Phenylene)bis(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl))pyrazoline (**5c**)

Dark yellow powder; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1312 (C–N), 1650 (C=N), 1689 (C=O), 3208 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.12 (s, 6H, 2 CH_3), 3.21 (dd, 2H, *J* 18.24, 9.88 Hz, 2 Hd), 3.89 (dd, 2H, *J* 18.28, 10.16 Hz, 2 Hc), 4.79 (m, 2H, 2 He), 5.87 (s, 2H, 2 H5), 7.36 (s, 4H, C_6H_4), 8.19 (s, 2H, 2 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.44 (2 CH_3), 43.40 (2 C-5′), 59.46 (2 C-4'), 99.12 (2 C-3), 103.63 (2 C-5), 126.62, 132.02 (C_6H_4–C), 153.69 (2 C-3′), 169.72 (2 C-6), 174.31 (2 C-2), 179.45 (2 C-4); ESI-MS: *m/z* 463.1 (M^+ + 1); anal. calcd. for $C_{24}H_{22}N_4O_6$: C, 62.39; H, 4.76; N, 12.12; found: C, 61.99; H, 5.06; N, 11.92.

1',1"-Phenyl-5',5"-(1,4-phenylene)bis(3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl))pyrazoline (**5d**)

Dark yellow solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1339 (C–N), 1649 (C=N), 1713 (C=O), 3423 (OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.26 (s, 6H, 2 CH_3), 3.32 (dd, 2H, *J* 18.88, 12.88 Hz, 2 Hd), 4.10 (dd, 2H, *J* 18.84, 12.28 Hz, 2 Hc), 5.28 (m, 2H, 2 He), 6.22 (s, 2H, 2 H5), 6.73-7.30 (m, 14H, 10Ar–H and 4H C_6H_4), 13.07 (s, 2H, 2 OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.58 (2 CH_3), 45.90 (2 C-5'), 61.73 (2 C-4'), 94.08 (2 C-3), 100.52 (2 C-5), 112.68, 119.38, 126.68, 135.42 (Ar–C, C_6H_4–C), 141.22 (2 C-3'), 161.25 (2 C-6), 163.41 (2 C-2), 183.12 (2 C-4); ESI-MS: *m/z* 615.2 (M^+ + 1); anal. calcd. for $C_{36}H_{30}N_4O_6$: C, 70.42; H, 4.89; N, 9.12; found: C, 70.62; H, 4.99; N, 9.02.

5',5"-(1,4-Phenylene)bis(3-(1,3-dimethyl-2,4,6-pyrimidine-trione-5-yl))pyrazoline (**5e**)

Light greenish powder; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1260 (C–N), 1626 (C=N), 1709 (C=O), 3212 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.24 (s, 12H, 4 N–CH_3), 3.47 (dd, 2H, *J* 18.50, 8.00 Hz, 2 Hd), 4.03 (dd, 2H, *J* 18.5, 9.48 Hz, 2 Hc), 4.77 (m, 2H, 2 He), 7.38 (s, 4H, C_6H_4), 8.22 (s, 2H, 2 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.08 (4 CH_3), 46.55 (2 C-5'), 58.62 (2 C-4'), 97.68 (2 C-5), 126.48, 130.41 (C_6H_4–C), 151.28 (2 C-3'), 168.78 (2 C-2), 179.05 (2 C-4, C-6); ESI-MS: *m/z* 523.1 (M^+ + 1); anal. calcd. for $C_{24}H_{26}N_8O_6$: C, 55.22; H, 4.98; N, 21.45; found: C, 55.52; H, 4.88; N, 21.05.

1',1"-Phenyl-5',5"-(1,4-phenylene)bis(3-(1,3-dimethyl-2,4,6-pyrimidinetrione-5-yl))pyrazoline (**5f**)

Green solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1237 (C–N), 1650 (C=N), 1738 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.10 (s, 12H, 4 N–CH_3), 3.73 (dd, 2H, *J* 19.40, 4.36 Hz, 2 Hd), 4.05 (dd, 2H, *J* 19.1, 9.8 Hz, 2 Hc), 5.06 (m, 2H, 2 He), 6.88-7.50 (m, 14H, 10Ar–H and 4H C_6H_4); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.23 (4 CH_3), 45.16 (2 C-5'), 63.03 (2 C-4'), 99.48 (2 C-5), 116.08, 129.05, 133.18, 134.64, 142.02 (Ar–C, C_6H_4–C), 166.01 (2 C-3'), 173.18 (2 C-2), 177.71 (2 C-4,C-6); ESI-MS: *m/z* 675.3 (M^+ + 1); anal. calcd. for $C_{36}H_{34}N_8O_6$: C, 64.15; H, 5.04; N, 16.61; found: C, 63.95; H, 4.84; N, 16.41.

5',5"-(1,4-Phenylene)bis(3-(2,4,6-pyrimidinetrione-5-yl))pyrazoline (**5g**)

Yellow powder; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1268 (C–N), 1634 (C=N), 1709 (C=O), 3121 (NH), 3216 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.47(dd, 2H, *J* 18.56, 8.04 Hz, 2 Hd), 4.03 (dd, 2H, *J* 18.16, 9.48 Hz, 2 Hc), 4.73 (m, 2H, 2 He), 7.38 (s, 4H, C_6H_4), 10.89 (s, 2H, 2 NH), 12.10 (s, 4H, 4 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 43.92 (2 C-5'), 55.62 (2 C-4'), 95.92 (2 C-5), 126.62, 130.12 (C_6H_4–C), 149.30 (2 C-3'), 166.65 (2 C-2), 179.01 (2 C-4, C-6); ESI-MS: *m/z* 467.2 (M^+ + 1); anal. calcd. for $C_{20}H_{18}N_8O_6$: C, 51.54; H, 3.86; N, 24.03; found: C, 51.14; H, 3.56; N, 23.73.

1',1"-Phenyl-5',5"-(1,4-phenylene)bis(3-(2,4,6-pyrimidine-trione-5-yl))pyrazoline (**5h**)

Orange solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1260 (C–N), 1622 (C=N), 1721 (C=O), 3184 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.78 (dd, 2H, *J* 8.60, 7.28 Hz, 2 Hd), 6.86 (m, 2H, 2 He), 7.25 (dd, 2H, *J* 15.96, 8.16 Hz, 2 Hc), 7.66-8.48 (m, 14H, 10Ar–H and 4H C_6H_4), 10.60 (s, 2H, 2 NH), 11.09 (s, 2H, 2 NH), 17.09 (s, 2H, 2 OH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 47.90 (2 C-5'), 65.21 (2 C-4'), 94.04 (2 C-5), 112.22, 119.18,

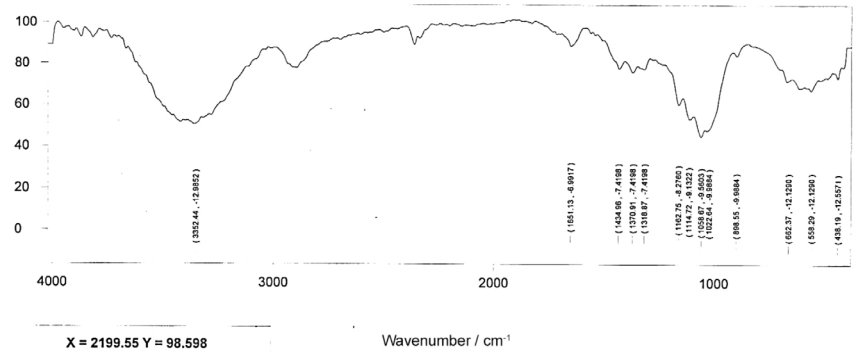


Figure 2. FT-IR spectra of cellulose sulfuric acid.

125.99, 129.18, 135.07, 144.75 (Ar–C, C_6H_4–C), 149.02, 149.71 (2 C-3'), 174.85 (2 C-2), 181.99 (2 C-4, C-6); ESI-MS: *m/z* 619.1 ($M^+ + 1$); anal. calcd. for $C_{32}H_{26}N_8O_6$: C, 62.19; H, 4.21; N, 18.12; found: C, 62.39; H, 4.41; N, 18.32.

5',5"-(1,4-Phenylene)bis(3-(2-mercapto-4,6-pyrimidinedione-5-yl))pyrazoline (**5i**)

Orange solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1151 (C=S), 1269 (C–N), 1629 (C=N), 1740 (C=O), 3180 (NH), 3220 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.17 (dd, 2H, *J* 18.76, 11.44 Hz, 2 Hd), 3.61 (dd, 2H, *J* 18.4, 12.92 Hz, 2 Hc), 4.27 (m, 2H, 2 He), 7.39 (s, 4H, C_6H_4), 9.99 (s, 2H, 2 NH), 10.89 (s, 4H, 4 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 42.02 (2 C-5'), 64.09 (2 C-4'), 99.48 (2 C-5), 126.62, 128.50 (C_6H_4–C), 160.53 (2 C-3'), 162.13 (2 C-4, C-6), 176.16 (2 C-2); ESI-MS: *m/z* 499.2 ($M^+ + 1$); anal. calcd. for $C_{20}H_{18}N_8O_4S_2$ C, 48.23; H, 3.61; N, 22.49; found: C, 47.93; H, 3.31; N, 22.19.

1',1"-Phenyl-5',5"-(1,4-phenylene)bis(3-(2-mercapto-4,6-pyrimidinedione-5-yl))pyrazoline (**5j**)

Green solid; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1141 (C=S), 1256 (C–N), 1630 (C=N), 1729 (C=O), 3264 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.06 (dd, 2H, *J* 14.88, 6.96 Hz, 2 Hd), 6.77 (dd, 2H, *J* 15.6, 7.8 Hz, 2 Hc), 7.09 (m, 2H, 2 He), 7.15-7.83 (m, 14H, 10Ar–H and 4H C_6H_4), 11.62 (s, 4H, 4 NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 43.85 (2 C-5'), 59.79 (2 C-4'), 99.49 (2 C-5), 120.01, 123.96, 128.86, 132.07, 137.69, 142.53 (Ar–C, C_6H_4–C), 152.04 (2 C-3'), 178.12 (2 C-4, C-6), 181.03 (2 C-2); ESI-MS: *m/z* 651.1 ($M^+ + 1$); anal. calcd. for $C_{32}H_{26}N_8S_2O_6$: C, 59.13; H, 4.99; N, 17.23; found: C, 58.73; H, 4.59; N, 16.83.

Results and Discussion

Characterization of the cellulose sulfuric acid (CSA)

The FT-IR spectrum of the catalyst (Figure 2) exhibited a broad peak for OH group at 3100-3600 cm^{-1}. The peaks from 1162-1058 cm^{-1} and at 898 cm^{-1} represented C–O stretching, C–C skeletal vibrations, and C_1–H ring stretching of the glucose unit, respectively. For sulfonic acid functional group, the peaks at 1162 and 1058 cm^{-1} of O=S=O group (asymmetric and symmetric stretching modes) had merged with the peaks of C–O stretching and C–C skeletal vibrations of glucose unit of cellulose moiety, whereas the peak for S–O stretching mode was present at 662 cm^{-1}.[27]

Powder XRD (Figure 3) of CSA showed characteristic diffraction peaks for cellulose moiety at 16.5, 22.5 and 34.5°.[28]

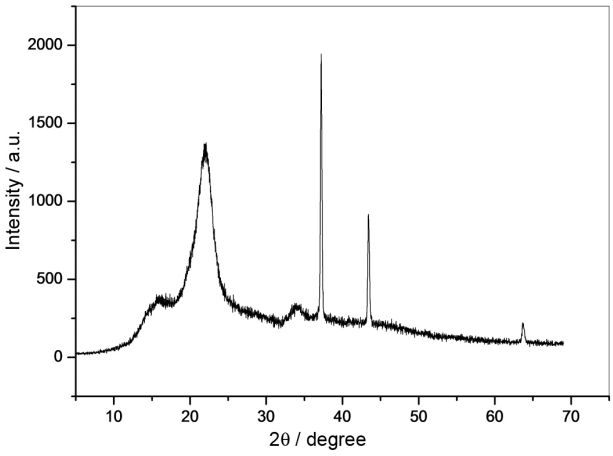


Figure 3. The powder XRD pattern of fresh catalyst.

The SEM images of CSA (Figure 4) showed smooth, compact and homogeneous fibrous surface.

EDX analysis (Figure 5) of CSA showed peaks for C, O and S elements.

To evaluate thermal stability of CSA, TG and DTA experiments were carried out and the thermograms are illustrated in Figure 6. For TG and DTA analysis the sample was heated up to 500 °C at a constant rate of 20 °C min^{-1} in the nitrogen atmosphere. The weight losses found from TG analysis measurements agreed fairly well with those expected for the decomposition of cellulose sulfuric acid to cellulose and sulfuric acid group. For this catalyst, the

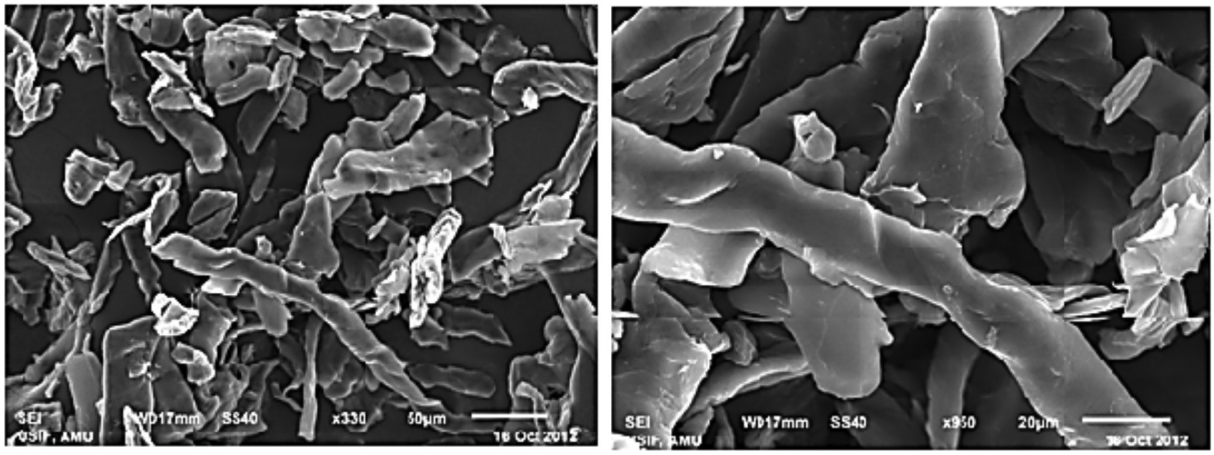


Figure 4. SEM images of the catalyst (CSA) at different magnifications.

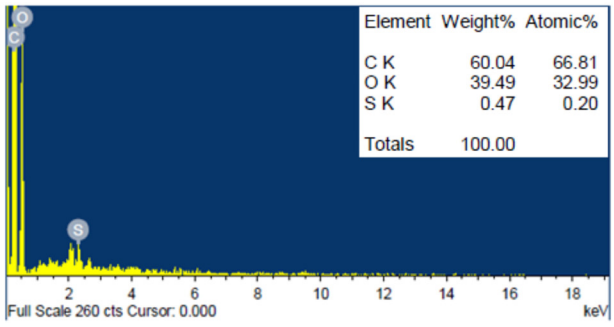


Figure 5. EDX analysis of the catalyst (CSA).

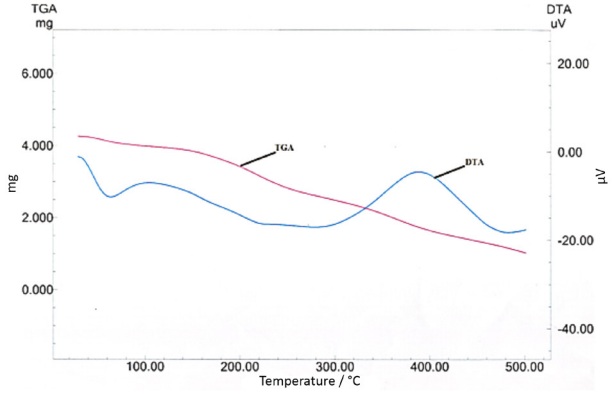


Figure 6. TG/DTA graph of cellulose sulfuric acid.

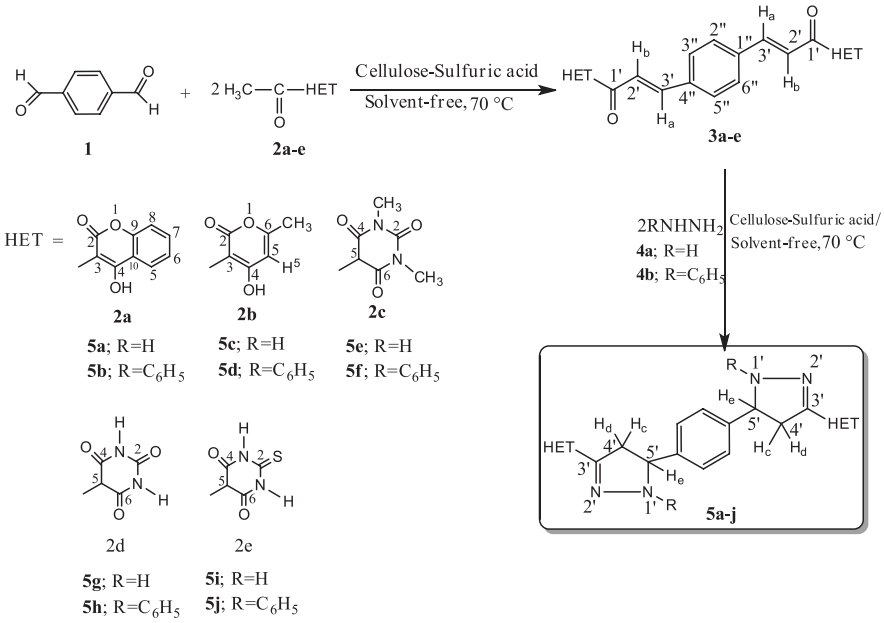
thermo gravimetric curve seems to indicate three-stage decomposition which was due to removal of physically adsorbed water (70-100 °C). Decomposition of the sulfonic functional group with rapid evolution of SO_3 or SO_2 between 200-330 °C took place and further gradually up to 500 °C which may be due to decomposition of cellulose showing mass loss of 34%. DTA measurement was performed in order to provide further evidence for the presence of the various species and evaluated their thermal behaviour (Figure 6). In the curve, the endothermic peak at lower temperature showed the removal of the physically adsorbed water from the material, while the endothermic peaks at higher temperatures (250 °C, 500 °C) represented the decomposition of cellulose sulfuric acid to cellulose and sulfuric acid group.

Synthesis of bis-chalcones (**3a-e**)

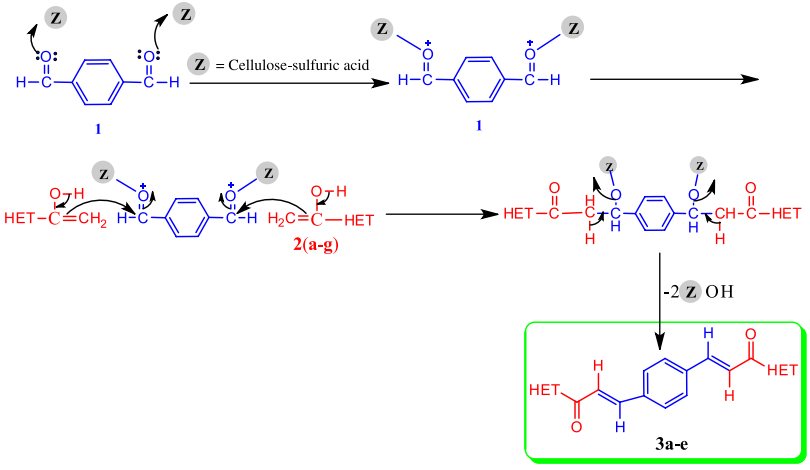
The synthesis of bis-chalcones (**3a**-**e**) was performed in a manner as outlined in Scheme 1. The structure of isolated bis-chalcones was verified by elemental analyses and spectroscopic data (FT-IR, ^{1}H NMR, ^{13}C NMR and MS). The infrared (IR) spectrum of **3a** exhibited the broad band for OH group at 3106 cm^{-1} and a sharp, strong band at 1719 cm^{-1} for coumarin carbonyl group. The carbonyl group of propenone moiety appeared as strong and sharp absorption band at 1668 cm^{-1} whereas band at 1620 cm^{-1} was assigned to carbon-carbon double bond of α,β-unsaturated system. The ^{1}H NMR spectrum showed trans olefinic protons Ha and Hb as ortho coupled doublets at δ 7.41 (J = 15.56 Hz) and δ 7.91 (J = 15.68 Hz), respectively. All other protons were present at their normal values. The ^{13}C NMR spectrum showed signal at δ 188.66 for α,β unsaturated carbonyl group whereas olefinic carbons C-2' and C-3' were present at δ 122.16 and 153.51, respectively. The other carbon signals appeared at their appropriate positions. Mass spectrum of **3a** showed molecular ion as $M^+ + 1$ peak at m/z 507. A plausible mechanism for the formation of (**3a**-**e**) is depicted in Scheme 2.

Synthesis of bis-pyrazolines (**5a-j**)

Bis-pyrazolines (**5a**-**j**) were synthesized employing (**3a**-**e**) (1.00 mmol) with hydrazine derivatives (**4a**-**b**) (2.00 mmol) in the presence of CSA under same reaction conditions (Scheme 1) (Table 1). The IR spectrum of **5a** showed two broad absorption bands at 3257 and 3201 cm^{-1}



Scheme 1. Synthetic route of bis-chalcones (**3a-e**) and bis-pyrazolines (**5a-j**).



Scheme 2. Plausible mechanism for the synthesis of bis-chalcones (**3a-e**).

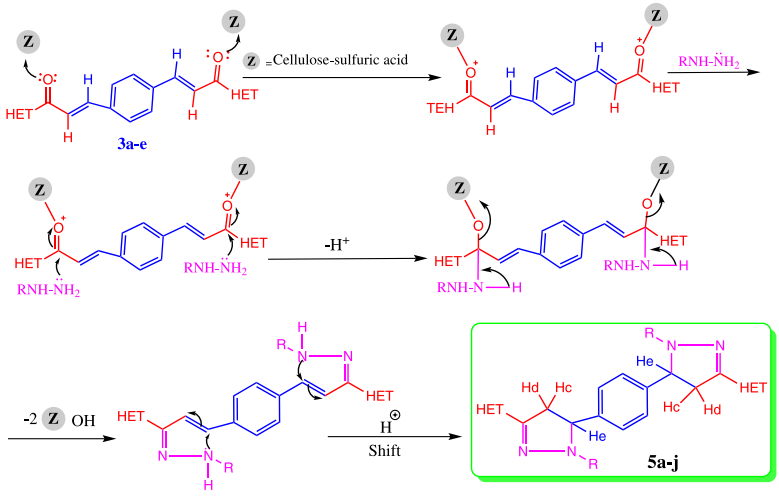
due to the presence of OH group of coumarin and NH group of pyrazoline moieties respectively whereas carbonyl absorption band for coumarin moiety was discernible at 1676 cm^{-1}. The absorbtion bands at 1612, 1314 cm^{-1} were assigned to C=N, C–N groups of pyrazoline moiety. In the ^{1}H NMR spectrum the presence of pyrazoline moiety was manifested by two doublets of doublets at δ 3.41 (Hd), 4.13 (Hc) and a multiplet at δ 4.90 (He). The NH proton of pyrazoline unit appeared as broad singlet at δ 8.24. The ^{13}C NMR spectrum showed signals at δ 44.85, 59.62, and 153.61 for C-5', C-4', and C-3' carbons of pyrazolines moiety respectively. The other peaks were present at their normal values and are mentioned in the experimental section. The mass spectrum of **5a** showed $M^+ + 1$ at *m/z* 535.1. A plausible mechanism for the formation of (**5a-j**) is depicted in Scheme 3.

Catalytic activity of CSA

The catalytic activity of CSA was explored by pursuing the synthesis of bis-chalcones and bis-pyrazolines. For optimization of appropriate reaction conditions, the reaction of terephthaldehyde (**1**) (1.00 mmol) with 3-acetyl-4-hydroxycoumarin (**2a**) (2.00 mmol) in the presence of CSA (0.06 g) under solvent-free conditions at 70 °C were chosen as a model reaction.

Solvent effect

We investigated the effect of different solvents in comparison with solvent-free condition on the reaction rate as well as yields of the products (Table 2). The data revealed



Scheme 3. Plausible mechanism for the synthesis of bis-pyrazolines (**5a**-**j**).

that maximum yield of the product (98%) in very short time period (3 min) was obtained only under solvent-free condition at 70 °C.

Table 2. Effect of various solvents versus the solvent-free condition for the model reaction[a]

entry	Solvent	Temperature / °C	time[b] / min	Yield[c] / %
1	THF	Reflux	1800	27
2	CH_3CN	Reflux	1440	35
3	$CHCl_3$	Reflux	960	44
4	CH_2Cl_2	Reflux	780	47
5	EtOH	Reflux	330	65
6	MeOH	Reflux	300	60
7	Isopropanol	Reflux	480	53
8	Acetic acid	Reflux	390	72
9	H_2O	Reflux	420	41
10	PEG-400	Reflux	240	54 (mixture)
11	Glycerol	Reflux	210	65 (mixture)
12	Solvent-free	25	72	17
13	Solvent-free	60	10	86
14	Solvent-free	70	3	98
15	Solvent-free	80	3	96

[a]Reaction conditions: terephthaldehyde (**1**, 1.00 mmol); 3-acetyl-4-hydroxycoumarin (**2a**, 2.00 mmol); catalyst (0.06 g); [b]reaction progress monitored by TLC; [c]isolated yields.

Comparison of CSA with other catalysts

In order to show the superiority of CSA, other sulfur analog acid catalysts were also used for the synthesis of **3a** (Table 3). The study revealed that the order of reactivity of various catalysts was PEG-sulfuric acid > camphor-sulfonic acid > silica-sulfuric acid > $NaHSO_4$-silica > xanthan-sulfuric acid > silica-sulfamic acid > *p*-toluene sulfonic acid > sulfuric acid in acetic acid. Thus, cellulose sulfuric acid is a more efficient and superior catalyst over other acidic catalysts in terms of time, yield and reaction condition.

Table 3. Comparison of catalytic activity of different catalysts for the model reaction[a]

entry	Catalyst	time[b] / min	Yield[c] / %
1	Cellulose-sulfuric acid	3	98
2	PEG-sulfuric acid[d]	48	81
3	Camphor-sulfonic acid[d]	78	77
4	Silica-sulfuric acid[d]	120	76
5	$NaHSO_4$-silica[d]	84	73
6	Xanthan-sulfuric acid[d]	90	71
7	Silica-sulfamic acid[d]	144	69
8	*p*-Toluene sulfonic acid[e]	90	68
9	Sulfuric acid in acetic acid[e]	168	57
10	Sulfamic acid[e]	–	Incomplete
11	Sulfanilic acid[e]	–	Incomplete
12	Cellulose[d]	–	Incomplete
13	No catalyst	No reaction	No reaction

[a]Reaction conditions: terephthaldehyde (**1**, 1.00 mmol); 3-acetyl-4-hydroxycoumarin (**2a**, 2.00 mmol); catalyst (0.06 g); solvent-free condition; 70 °C; [b]reaction progress monitored by TLC; [c]isolated yields; [d]0.120 g of catalyst; [e]0.1 mmol of catalyst.

Effect of amount of CSA

Generally, the rate of reaction and yield increases over the amount of catalyst. To optimize the reaction conditions, the model reaction was studied in the presence of varying amounts of catalyst (Figure 7). In order to obtain the best result, the optimum amount of catalyst turned out to be 0.06 g. On increasing the loading to 0.08 g, no significant

improvement in the yield was observed, whereas, decreasing the amount of catalyst to 0.04 g resulted in lowering of the yield.

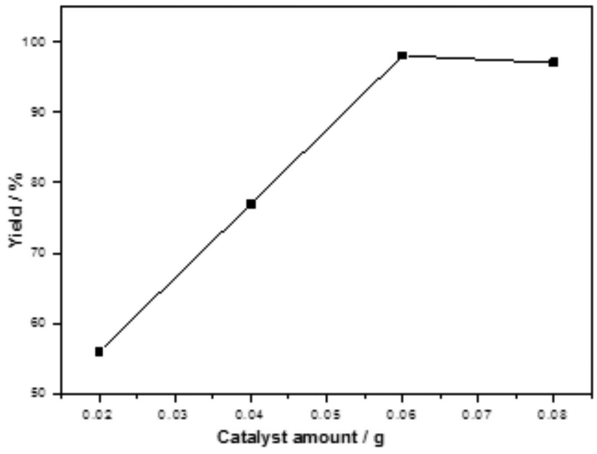


Figure 7. Effect of catalyst loading on the model reaction.

Reusability of CSA

The reusability of the catalyst under solvent-free condition was evaluated using model reaction of terephthaldehyde (**1**) with 3-acetyl-4-hydroxycoumarin (**2a**) in the presence of CSA (0.06 g) (Figure 8). After completion of the reaction, the catalyst was recovered by filtration and was than reused for eight cycles adopting the identical protocol with a minor loss of catalytic activity.

The identity of the recovered catalyst was checked by powder XRD (Figure 9) and SEM analysis (Figure 10). The XRD pattern was similar to that of fresh catalyst with some low intensity of peaks which may be due to the catalyst deactivation after eight runs. The SEM image revealed intact morphology after eight runs. These data establish that CSA is not damaged upon its reuse as a heterogeneous catalyst.

Under these optimized reaction conditions the scope and generality of the current protocol was further demonstrated

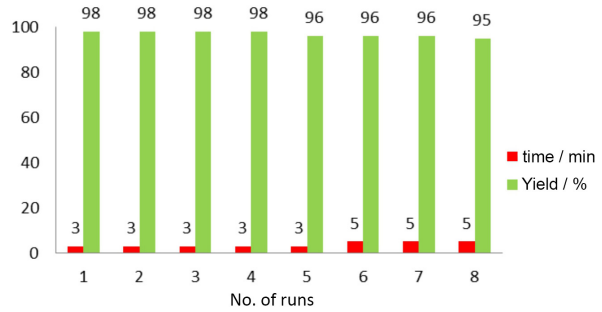


Figure 8. Recycling data of CSA for model reaction.

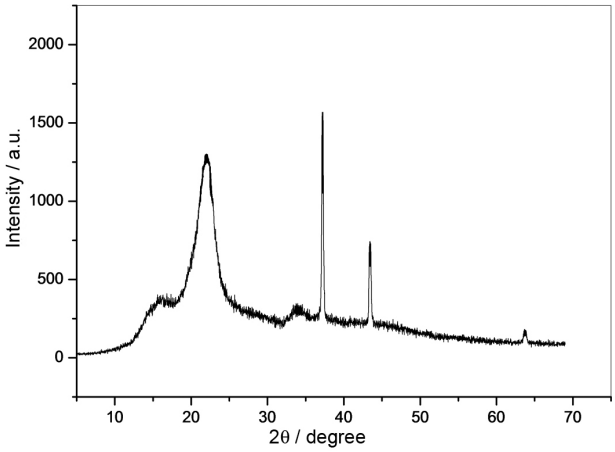


Figure 9. Powder XRD pattern of recovered catalyst after eight runs.

by the reaction of terephthaldehyde (**1**) with different cyclic active methyl compounds (**2a**-**e**) under solvent-free conditions. All the reactions proceeded smoothly and the reaction was completed within 3-9 min to afford the products (**3a**-**e**) in excellent yields (95-98%) (Table 1).

Conclusion

In conclusion, we have developed an expedient, highly efficient, atom economical and simple protocol for the synthesis of novel heterocyclic bis-chalcones and

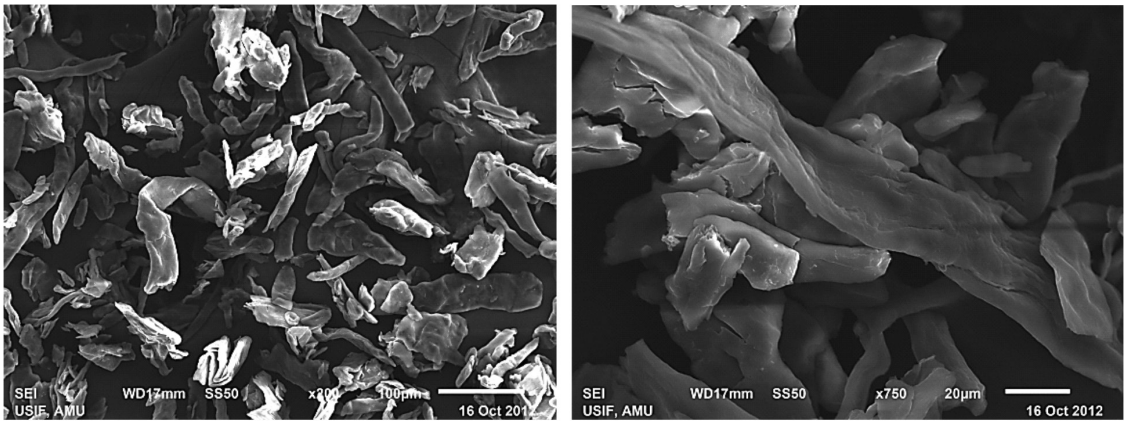


Figure 10. SEM image of recovered catalyst after eight runs.

corresponding pyrazoline derivatives in excellent yields using cellulose sulfuric acid as an inexpensive biopolymer-based solid acid catalyst under solvent-free conditions. Prominent advantages of this green method are broad scope, operational simplicity, practicability, excellent yields, shorter reaction time, economic viability, easy work-up, and recyclability of the catalyst. We believe that this protocol will be a more practical alternative to the other existing methods.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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References

1. Yang, X.-H.; Wen, Q.; Zhao, T.-T.; Sun, J.; Li, X.; Xing, M.; Lu, X.; Zhu, H.-L.; *Bioorg. Med. Chem.* **2012**, *20*, 1181.
2. Hsieh, C.-T.; Hsieh, T.-J.; El-Shazly, M.; Chuang, D.-W.; Tsai, Y.-H.; Yen, C.-T.; Wu, S.-F.; Wu, Y.-C.; Chang, F.-R.; *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3912.
3. Zhang, H.; Liu, J.-J.; Sun, J.; Yang, X.-H.; Zhao, T.-T.; Lu, X.; Gong, H.-B.; Zhu, H.-L.; *Bioorg. Med. Chem.* **2012**, *20*, 3212.
4. Reddy, M. V. B.; Shen, Y.-C.; Ohkoshi, E.; Bastow, K. F.; Qian, K.; Lee, K.-H.; Wu, T.-S.; *Eur. J. Med. Chem.* **2012**, *47*, 97.
5. Raj, C. G. D.; Sarojini, B. K.; Ramakrishna, M. K.; Ramesh, S. R.; Manjunatha, H.; *Med. Chem. Res.* **2012**, *21*, 453.
6. Alvim, H. G. O.; Fagg, E. L.; de Oliveira, A. L.; de Oliveira, H. C. B.; Freitas, S. M.; Xavier, M.-A. E.; Soares, T. A.; Gomes, A. F.; Gozzo, F. C.; Silva, W. A.; Neto, B. A. D.; *Org. Biomol. Chem.* **2013**, *11*, 4764.
7. Dhar, D. N.; *Chemistry of Chalcones and Related Compounds,* 2nd ed.; Wiley-VCH: New York, USA, 1981.
8. Mobinikhaledi, A.; Kalhor, M.; Jamalifar, H.; *Med. Chem. Res.* **2012**, *21*, 1811.
9. Jahng, Y.; Zhao, L.-X.; Moon, Y.-S.; Basnet, A.; Kim, E.-K.; Chang, H. W.; Ju, H. K.; Jeong, T. C.; Lee, E.-S.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2559.
10. Climent, M. J.; Corma, A.; Iborra, S.; Velty, A.; *J. Catal.* **2004**, *221*, 474.
11. Sebti, S.; Solhy, A.; Smahi, A.; Kossir, A.; Oumimoun, H.; *Catal. Commun.* **2002**, *3*, 335.
12. Narender, T.; Reddy, K. P.; *Tetrahedron Lett.* **2007**, *48*, 3177.
13. Varma, R. S.*; Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2006**, *45*, 2305.
14. van Santen, R. A.; Neurock, M.; *Molecular Heterogeneous Catalysis: A Conceptual and Computational Approach;* Wiley-VCH: Cambridge, 2006.
15. Lancaster, M. In *Handbook of Green Chemistry and Technology*; Clark, J. H.; Macquarrie, D. J., eds.; Blackwell: Abingdon, 2002.
16. Klemm, D.; Heublein, B.; Fink, H-P.; Bohn, A.; *Angew Chem., Int. Ed.* **2005**, *44*, 3358.
17. Mofakham, H.; Hezarkhani, Z.; Shaabani, A.; *J. Mol. Catal. A: Chem.* **2012**, *360*, 26.
18. Kuarm, B. S.; Madhav, J. V.; Rajitha, B.; Reddy, Y. T.; Reddy, P. N.; Crooks, P. A.; *Synth. Commun.* **2011**, *41*, 662.
19. Rahmatpour, A.; *React. Funct. Polym.* **2011**, *71*, 80.
20. Safari, J.; Banitaba, S. H.; Khalili, S. D.; *J. Mol. Catal. A: Chem.* **2011**, *335*, 46.
21. Reddy, B. V. S.; Venkateswarlu, A.; Madan, Ch.; Vinu, A.; *Tetrahedron Lett.* **2011**, *52*, 1891.
22. Siddiqui, Z. N.; Khan, T.; *RSC Adv.* **2014**, *4*, 2526.
23. Nohara, A.; Umetani, T.; Sanno, Y.; *Tetrahedron* **1974**, *30*, 3553.
24. Jursic, B. S.; Neumann, D. M.; *Tetrahedron Lett.* **2001**, *42*, 8435.
25. Eisenhauer, H. R.; Link, K. P.; *J. Am. Chem. Soc.* **1953**, *75*, 2044.
26. Shaabani, A.; Maleki, A.; *Appl. Catal., A* **2007**, *331*, 149.
27. Singare, P. U.; Lokhande, R. S.; Madyal, R. S.; *Open J. Phys. Chem.* **2011**, *1*, 45.
28. Wu, Y.; Fu, Z.; Yin, D.; Xu, Q.; Liu, F.; Lu, C.; Mao, L.; *Green Chem.* **2010**, *12*, 696.

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