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One Pot Synthesis of 1, 2-Disubstituted Benzimidazole Derivatives Using C-SO_3H Catalyst

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Abstract

We have described an efficient method for the synthesis of 1,2- disubstituted benzimidazole derivatives from various aldehydes and *o*-phenylenediamine using ethanol as a solvent using C-SO_3H as a catalyst at reflux conditions. All the synthesized compounds were characterized by FT-IR, ^1H NMR and ^{13}C NMR techniques. The thermally and chemically stable, metal free, functionalized green C-SO_3H catalyst was obtained by *in-situ* partial carbonization and sulfonation of glycerol with sulfuric acid and the nature of the catalyst was confirmed by SEM, EDX and XRD techniques.

Keywords: Carbon-SO_3H, Green catalyst, 1,2 disubstituted Benzimidazoles, Heterogenous catalyst.

Introduction

In recent days, the reusable heterogeneous solid acid catalysts are frequently used as the replacement for liquid-based acid catalysts [1]. The synthesis or any kind of chemical reactions which are based on homogeneous medium like sulphuric acid involves high energy consumption and a complicated separation procedure of the catalyst from the reaction mixture [2]. Sulphuric acid is the most important industrially by needed chemical for many organic transformation reactions such as nitration, sulfonation, esterification, and electrolysis etc. and the excessive usage of large amount of H_2SO_4 causes severe environmental hazards [3]. C-SO_3H is considered as a replacement for liquid acid catalysts that overcome environmental problems. SO_3H loaded carbon heterogeneous catalyst was prepared in many ways like simple sulphonation of sucrose [4], glucose [5] and starch [6] or by incomplete carbozation followed by sulfonation of carbohydrates such as sugar or cellulose. Here in we report the synthesis of C-SO_3H solid catalyst from very low-cost material, glycerol which is a by-product from the production of biodiesel. This SO_3H loaded carbon catalyst has distinct properties such as high mechanical and thermal stability, good pore structure, insoluble in organic solvents like methanol, ethanol, hexane, chloroform as well as water [7-9]. Due to the above advantages of C-SO_3H heterogeneous catalyst, researchers have recommended this material in the place of liquid H_2SO_4 in many organic transformation reactions, electrocatalysis, water treatment, CO_2 capture and a few more catalysis reactions [10-19]. Nitrogen and oxygen atoms bearing heterocyclic compounds are highly abundant in nature and they have varieties of application in bioactivities particularly in pharmaceuticals and agrochemicals. 1,2-Disubstituted benzimidazole based derivatives are core structural heterocyclic compounds of most of the drugs and natural products [20-22]. Benzimidazole based core structures are present in commercial drugs like

Atacand, Nexium, Micardis, Protonix and Vermox [23-25]. Benzimidazole derivatives are also found to act as potent cyototoxic antitumor agents [26,27] and DNA binding agents [28].

Experimental methods

Reagents and common solvents such as ethanol, methanol, acetone, dichloromethane, tetrahydrofuran, acetonitrile, etc., were purchased from commercial sources in their high purity and used as received. Reactions were monitored by TLC using silica gel 60 F_{254} aluminium sheets with hexane/ethyl acetate as the eluting solvent system. Melting points were determined with an electro-thermal apparatus by open capillary method and are uncorrected. NMR spectra were recorded on a BRUKER DRX-400 MHz spectrometer in DMSO-d_6 and δ values are expressed in ppm using tetramethyl silane (TMS) as an internal standard.

Preparation of C–SO_3H

A mixture of glycerol (15 g) and concentrated H_2SO_4 (45 g) was taken in a 500-ml beaker and gently heated on a hotplate from ambient temperature to 190 °C with constant stirring to facilitate *in situ* partial carbonization and sulfonation. The reaction mass was allowed at that temperature for about 30 minutes till the foaming was ceased to obtain the solid C-SO_3H catalyst. The catalyst was cooled to room temperature and washed with water under agitation until the washed water remains neutral to pH paper. The product was filtered and dried at 110 °C for 3 h to get glycerol-based C-SO_3H catalyst.

C-SO_3H catalyst characterization

To investigate morphological and elemental composition the C-SO_3H catalyst, scanning electron microscopy (SEM) analysis integrated with EDX spectroscopy was performed. FT-IR spectra was recorded on Bruker FT-IR27 spectrophotometer using KBr optics. The particle size was analyzed by Dynamic light scattering technique and X-ray diffraction study was analyzed by powder X-ray diffractometer.

General experimental procedure for the synthesis of 1,2-disubstituted benzimidazole derivatives:

In a 50 mL RB flask containing ethanol (5 mL), a mixture of aromatic aldehydes **1a-e** (2 mmol), *o*-phenylene diamine **2** (1 mmol) and C-SO_3H (50 mg) were added. The resulting mixture was allowed to stir at reflux condition for a specified time given in table 4 leading to the formation of 1,2-disubstituted benzimidazole derivatives (**3a-e).** After completion of the reaction (monitored by TLC with mobile phase ethyl acetate and n-hexane), the reaction mixture was cooled to ambient temperature and filtered along with the catalyst. The product was recrystallized using hot ethanol. The catalyst has been recovered by washing with ethyl acetate and reused successively. All the synthesized compounds were characterized with FT-IR, ^{1}H NMR and ^{13}C NMR techniques.

Spectral data for synthesized 1,2-disubstituted benzimidazole derivatives

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole (4a):

Colour: Yellow; ^{1}H NMR (400 MH_Z, DMSO-d_6): δ= 8.13-6.96 (m, 12H, Ar-H), 5.55 (s, 2H, CH_2); ^{13}C NMR (100MH_Z, DMSO-d_6): 167.1, 152.4, 150.3, 141.9, 138.4, 135.7, 132.7, 131.6, 131.2, 129.8, 129.5, 129.2, 128.8, 128.4, 128.1, 124.0, 123.6, 119.4, 115.4, 47.3; FT-IR (KBr): 3040, 2844, 1991, 1678, 1592 cm^{-1}.

1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1*H*-benzo[*d*] imidazole (4b):
Colour: Pale yellow; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.20-7.00 (m, 12H, Ar-H), 5.59 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 152.24, 150.6, 143.0, 136.4, 136.3, 135.2, 134.9, 132.5, 131.5, 131.2, 129.5, 129.4, 128.6, 128.4, 123.4, 122.9, 122.7, 119.8, 111.5, 47.3; FT-IR (KBr): 3052, 2754, 1888, 1645, 1573 cm^{-1}.

1-(4-Fluorobenzyl)-2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazole (4c):
Colour: Pale yellow; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.25-7.01 (m, 12H, Ar-H), 5.57 (s, 2H, CH_2); ^{13}C (100MHz, DMSO-d_6): 162.3, 152.8, 150.9, 143.1, 136.3, 133.6, 131.9, 129.2, 128.6, 127.2, 127.0, 123.3, 122.7, 119.7, 116.5, 116.4, 116.2, 115.9, 111.5, 47.2; FT-IR (KBr): 3050, 2950, 1887, 1601, 1532 cm^{-1}.

1-(3-nitrobenzyl)-2-(3-nitrophenyl)-1*H*-benzo[d]imidazole (4d)
Colour: Pale brown; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.67-7.30 (m, 12H, Ar-H), 5.80 (s, 2H, CH_2); ^{13}C NMR (100MHz, DMSO-d_6): 151.8, 149.9, 149.2, 148.7, 143.3, 139.9, 136.8, 136.1, 135.7, 133.5, 133.3, 131.7, 131.4, 131.4, 129.3, 125.3, 125.0, 123.6, 121.6, 47.7; FT-IR (KBr): 3084, 2915, 1918, 1613, 1523 cm^{-1}.

1-(2-Nitrobenzyl)-2-(2-nitrophenyl)-1*H*-benzo[*d*] imidazole (4e):
Colour: Pale yellow; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.17-7.51 (m, 12H, Ar-H), 5.71 (s, 2H, CH_2) ;^{13}C NMR (100MHz, DMSO-d_6): 149.7, 148.6, 147.9, 146.9, 134.8, 134.2, 134.0, 133.7, 132.7, 129.5, 128.9, 128.2, 126.0, 125.0, 124.3, 123.4, 123.0, 122.6, 120.2, 45.6; FT-IR (KBr): 3057, 2839, 2636, 1845, 1608, 1521 cm^{-1}.

Results and Discussion

C-SO_3H Catalytic study

Thermally and chemically stable metal free glycerol-based carbon catalyst was an amorphous material which showed more effective catalytic activity because of large -SO_3H group density on its surface area. The C-SO_3H catalyst was analyzed by FT-IR spectroscopy in the range of 500-4000 cm^{-1}. In figure 1, the broad vibration band at 3401 cm^{-1} indicates -OH stretching vibrations of sulfuric acid, the bands at 1587 cm^{-1} and 1026 cm^{-1} representing the symmetric and asymmetric stretching of SO_2 group, which proves the presence of sulfonic groups on the catalyst. The powder X-ray diffractogram of C-SO_3H catalyst was examined in figure 6. It exhibits two broad peaks in the diffraction of 2θ =25°, which shows the amorphous nature of the C-SO_3H catalyst. The particle size and distribution size of C-SO_3H catalyst using DLS technique in the suspension of solvent dispersed medium are shown in-between 800-900 nm (figure 4).

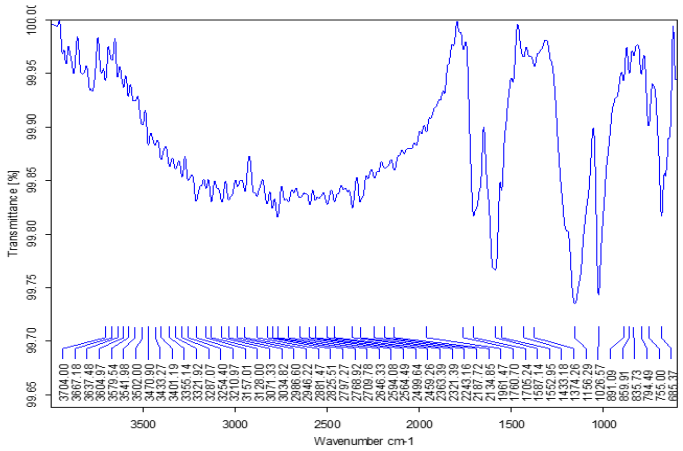


Figure1. FT-IR spectrum of fresh C-SO_3H catalyst

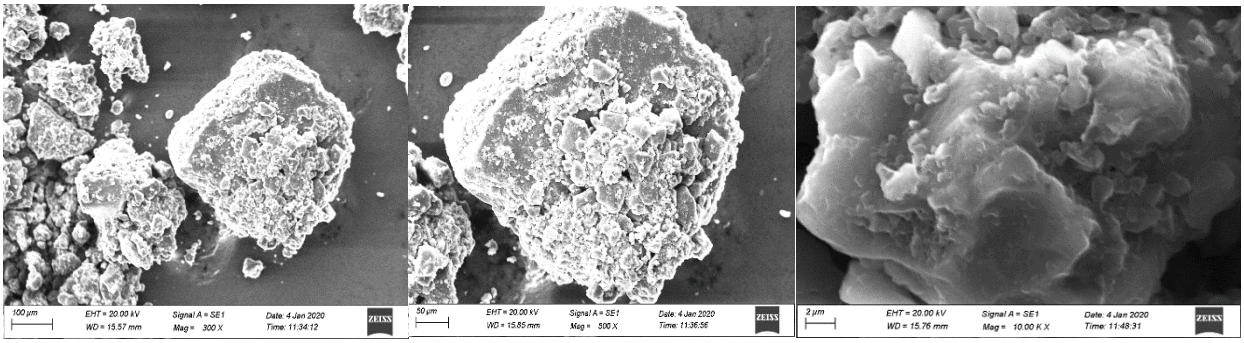


Figure 2. SEM images of C-SO_3H catalyst

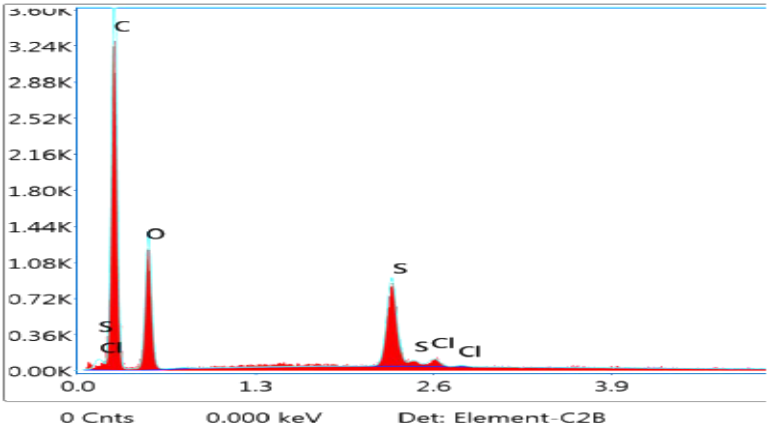


Figure 3. EDX image of C-SO_3H catalyst

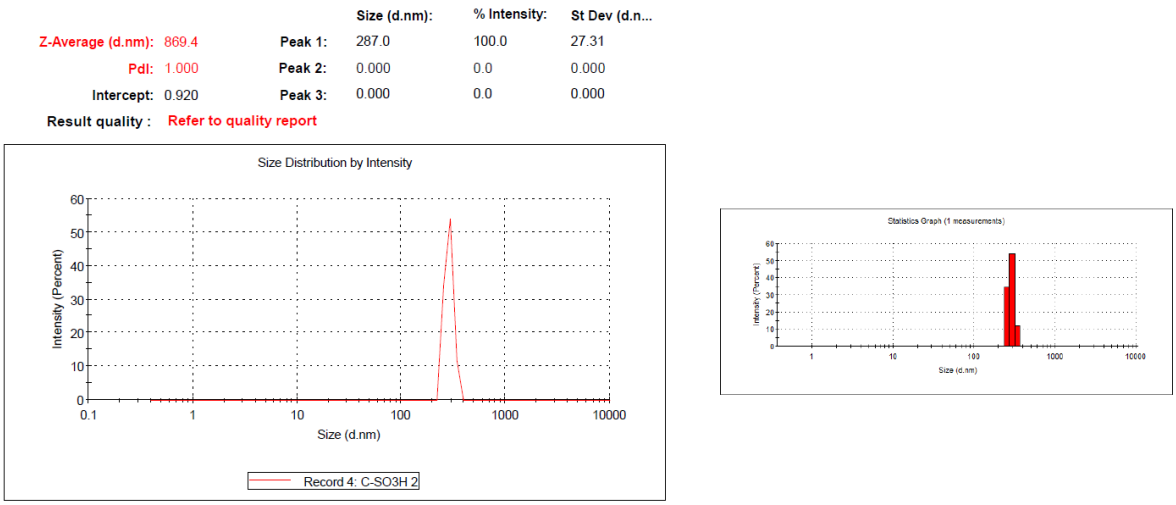


Figure 4. DLS particle analysis of C-SO_3H catalyst

One pot multicomponent reaction of ortho phenylene diamine (OPD) and *para*-chloro benzaldehyde as a model reaction for the synthesis of 1,2 disubstituted benzimidazole in various solvents, including methanol, ethanol, tetrahydrofuran, chloroform, dichloromethane, 1,2 dioxane, toluene and acetonitrile at room temperature condition has been studied (Table 1, entry 1-8), where the reaction in ethanol solvent medium provided a good yield (72%) compared to other solvents.

Table 1. Optimization of suitable solvent[a]

Entry	**Solvent**	**Time (min)**	**[b]Yield (%)**
1	Methanol	25	60
2	Chloroform	32	56
3	Dichloromethane	28	54
4	Ethanol	18	72
5	DMF	19	65
6	1,2 Dioxane	20	61
7	Acetonitrile	25	59
8	Toluene	40	45

[a]p-chlorobenzaldehyde (2 mmol), orthophenylene diamine (1 mmol), different solvents (5 ml) at room temperature. [b]Isolated yield

Further, to optimize the temperature, the above reaction (formation of product 3a) was conducted at different temperatures such as room temperature, 50 ºC, 60 ºC, 70 ºC and reflux. When the reaction was carried out at reflux condition, the reaction was completed in 9 min with the yield 80% and the same reaction was completed in 18 min with the yield of 72% yield at room temperature (Table 2).

Table 2. Optimization of suitable temperature[a]

Entry	Temperature	Time (min)	[b]Yield (%)
1	RT	18	72
2	50	15	75
3	60	12	77
4	70	09	78
5	Reflux	09	80

[a]p-chlorobenzaldehyde (2 mmol), orthophenylene diamine (1 mmol), ethanol (5 ml) stirred at different temperatures. [b]Isolated yield

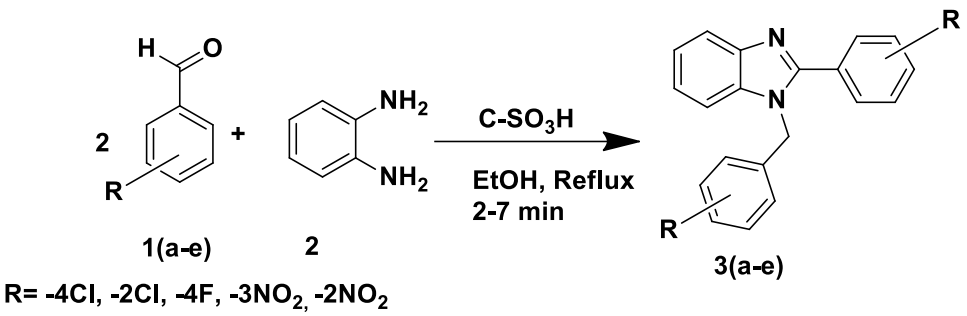
Next to optimize the amount of catalyst, the same reaction (formation of product 3a) was carried out with different milligrams of C-SO_3H catalyst such as 20mg, 30 mg, 50 mg, 80 mg and 100 mg where the reaction gave very good yield with 50 mg of catalyst providing 96% yield at very short reaction time (2 min) (Table 3).

Table 3. Optimization of suitable mg of catalyst[a]

Entry	Catalyst (mg)	Time (min)	[b]Yield (%)
1	-	09	80
2	20mg	08	86
3	30mg	06	90
4	50mg	02	96
5	80mg	02	96
6	100mg	02	96

[a]p-chlorobenzaldehyde (2 mmol), orthophenylene diamine (1 mmol), ethanol (5 ml) and C-SO_3H, stirred at reflux temperature. [b]Isolated yield

Thus, we introduced a novel synthetic method for 1,2, disubstituted benzimidazole derivative (3a-h) by simply refluxing various aldehydes and *o*-phenylenediamine, with C-SO_3H catalyst in ethanol, obtaining the target product with good to excellent yields (85-96%) (Scheme 1). FT-IR spectrum of compound 3a (Table 4, Entry 1) shows a band at 3040 cm^{-1} that indicates the presence of C=C-H and a sharp band at 2844 cm^{-1} corresponding to the alkane group. A band at 1991 cm^{-1} denotes the C–C of aromatic and band at 1678 cm^{-1} denotes alkene group. The peak at 1592 cm^{-1} indicates the presence of –C=N–stretching. In the ^1H NMR spectrum of the compound 3a, multiplets from δ 8.13 – 6.96 ppm indicate the existence of the aromatic protons. A sharp singlet at δ 5.55 shows the presence of –CH_2 protons. In the ^{13}C NMR spectrum of compound 3a, the signals for aromatic carbons are found in the range, δ 115.4 to 167.17 ppm and the signal for CH_2 appeared at 47.3 ppm.



Scheme 1. Synthesis of 1,2-disubstituted benzimidazole derivatives

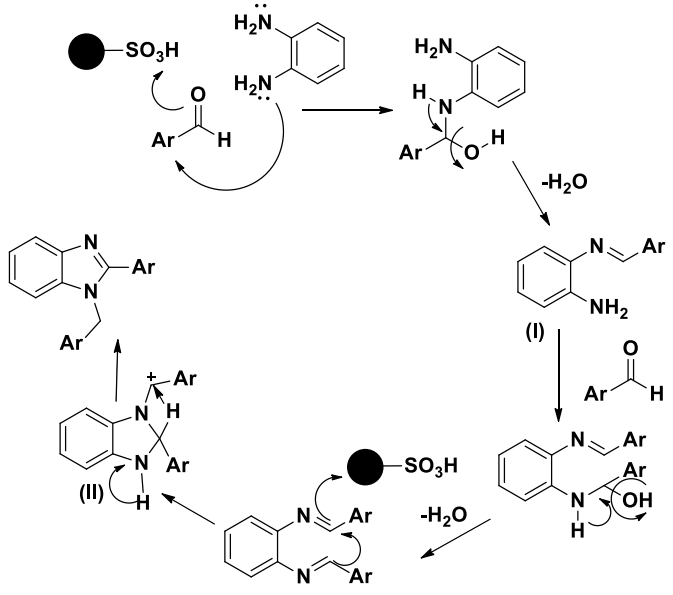
Table 4. Synthesis of 1,2-disubstituted benzimindazole[a]

Entry	R	OPD	Product	Time (min)	[b]Yield (%)
1.	4-Cl	OPD	3a	2	96
2.	2-Cl	OPD	3b	5	92
3.	4-F	OPD	3c	7	90
4.	2-NO_2	OPD	3d	3	94
5.	3-NO_2	OPD	3e	3	95

[a]Reaction condition: Substituted aldehydes (1 mmol), orthophenylene diamine (OPD), C-SO_3H (50 mg) in ethanol solvent, reflux condition. [b]Isolated yield.

Plausible mechanism approach for the formation of 1, 2-disubstituted benzimidazole derivatives.

A plausible mechanism for the formation of the product is described in scheme 2. Aromatic aldehyde was activated by C-SO_3H during the reaction. Initially Schiff's base formation was occurred between arylenediamine and substituted aromatic aldehydes (I) followed by cyclization and 1,3 hydride transfer (II) to form the final product, 1,2-disubstituted benzimidazole (Scheme 3).



Scheme 2. Possible mechanism in the formation of 1, 2-disubstituted benzimidazole derivatives

Reusability

The successive reusability of the recovered C-SO_3H catalyst was examined by the scheme 1 under the optimized conditions. The C-SO_3H catalyst gave 96 to 90 % of yield of the products without any loss of its effectiveness even after 6th run. The activity of the catalyst after the 7th run was reduced for the formation of the product as shown in figure 7. The recovered C-SO_3H catalyst was further analyzed by X-ray diffraction and FT-IR studies (Table 6).

FT-IR and X-ray diffraction studies are shown in figures 5 and 6. The FT-IR spectra of 4th and 8th run C-SO_3H catalyst show the broad vibration band at 3394 cm^{-1} indicating -OH stretching vibrations of sulfonic acid, the band at 1686 and 1037 cm^{-1} representing the symmetric and asymmetric stretching of SO_2 group which proves the sulfonic group on C-SO_3H material. These values are well coincided with pure (unrecycled) C-SO_3H catalyst (figure 7). X-ray diffraction patterns of the fresh and after recovery of C-SO_3H catalyst reveal the carbon particles remain in the same range 2θ=25°-30° attributed to the amorphous nature even after 8th run.

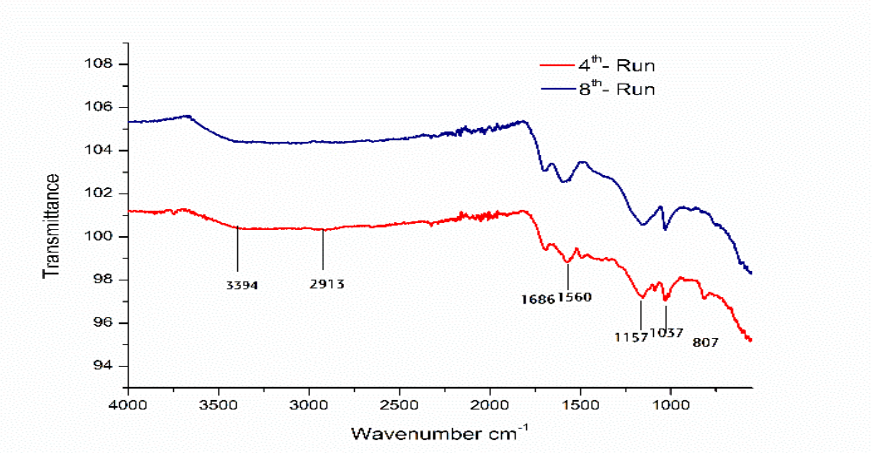


Figure 5. FT-IR spectura of recycled C-SO_3H catalyst

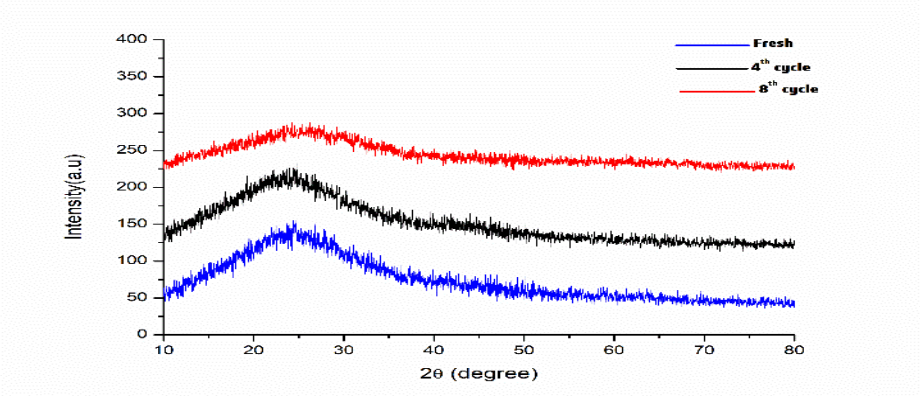


Figure 6. XRD of recycled C-SO_3H catalyst

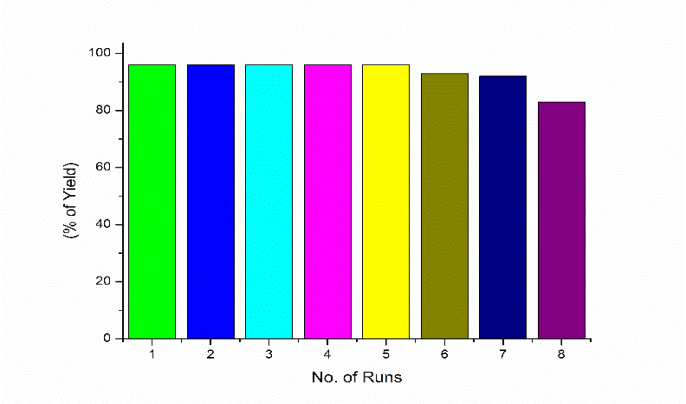


Figure 7. Percentage of product yield recycled C-SO_3H catalyst

Table 6. Reusability of the C-SO_3H catalyst[a]

Entry	Cycle	[b]Yield (%) 1,2 disubstituted benzimidazole
1	I	96
2	II	96
3	III	96
4	IV	96
5	V	96
6	VI	93
7	VII	92
8	VIII	82

[a]Reaction condition: Substituted aldehydes (1 mmol), orthophenylene diamine (OPD), C-SO_3H (50 mg) reflux condition. [b]Isolated yield.

Conclusion

Finally, we have concluded a green and efficient methodology for the synthesis of 1,2-disubstituted benzimidazole derivatives *via* one step, two component reaction using reusable C-SO_3H as an effective solid acid catalyst derived from glycerol at reflux condition in ethanol medium. Catalyst reusability, mild reaction conditions, ease of procedure and good yields are the advantages of this method.

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