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Sulfamic acid supported on cellulose as a biodegradable and recyclable heterogeneous catalyst for the synthesis of tetrahydrobenzo xanthene derivatives

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Abstract

Cellulose bonded N-propyl diethylene tetra sulfamic acid (CBPDETSA) was successfully applied as a green and recyclable acidic catalyst for the synthesis of tetrahydrobenzo [a] xanthene-11-one as an important class of potentially bioactive compounds. The products are obtained by the coupling of 2-naphtol, cyclohexadione and aldehyde derivatives in good to high yields (70- 92%) under solvent-free conditions. The reactivity of different aromatic aldehydes was influenced by the nature and position of the substituents on the aromatic ring. The benzaldehyde derivatives having an electron-withdrawing substituent were highly reactive and gave the products in excellent yields. Also, the catalyst could be recovered by filtration and subjected to further reaction processes. The results show that the yield of product after five runs was only slightly reduced.

Keywords: Heterogeneous catalyst; cellulose; xanthene; solvent-free; CBPDETSA.

Introduction

In recent years, there has been a rapid growth in the development of novel polymer supported compounds such as supported catalysts, reagents and scavengers. Preparing heterogeneous catalysts by immobilizing the

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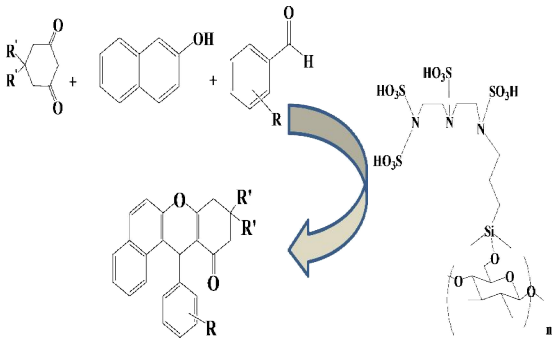
homogenous precursors on solid support is one of the important routes for developing novel heterogeneous catalysts. In most of these cases, the immobilized catalysts prepared in such a way could provide advantages over their unsupported counterparts in terms of easy separation, low toxicity, moisture resistance, air tolerance, easy handling, reusability [1,2]. In this regard, natural biopolymers are attractive candidates in the search of support catalysts [3]. Biopolymers such as alginate, gelatin, starch and chistosan derivatives have been used as support for catalytic applications [4-8]. It is well-known that cellulose is the most abundant natural marital in the world, biodegradable substrate and a renewable resource which make it unique for conventional organic or inorganic in catalytic applications [9]. On a different note, xanthene scaffold constitute an important pharmaco phoric moiety, which exhibits important biological effects such as antiviral, antibacterial and anti-inflammatory activities [10, 11]. In addition, various derivatives of xanthenes are used as dyes in laser technology [12], and pH-sensitive fluorescent materials for the visualization of bio molecular assemblies [13]. Many benzoxanthene derivatives are also potent non-peptidic inhibitors of recombinant human calpain I and novel CCR1 receptor antagonists [14]. The synthesis of xanthenes and benzo xanthenes has been carried out by different methods [15-19]. However, most of these methodologies involve harsh conditions or longer reaction time leaving considerable scope for development of further clean, facile and efficient process for the synthesis of these important molecules. Therefore, the development of new synthetic methods for the efficient preparation of heterocycles containing xanthene fragment is an interesting challenge. In continuation of our researches on the application of heterogeneous and reusable solid catalysts in organic synthesis [20–23], recently we applied cellulose bonded *N*-propyl diethylene tetrasulfamic acid (CBPDETSA) in the synthesis of tetrahydrobenzo [a] xanthenes-11-one by the coupling of 2-naphtol, cyclohexadione and aldehyde derivatives (Scheme 1).



Scheme 1. Preparation of benzo xanthenes by CBPDETSA

Experimental

Chemicals

Reagents and solvents were purchased from Merck and Fluka chemical companies. Purity determination of the products was accomplished by TLC on silica-gel polygram SILG/UV 254 plates. Melting points were measured on an Electro thermal 9100 apparatus. IR spectra were taken on a Perkin Elmer 781 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DPX-250 Avance instrument at 250 MHz and 62.9 MHz in $CDCl_3$ or DMSO-d_6 with chemical shift given in ppm relative to TMS as internal standard.

Preparation of catalyst

Preparation of cellulose bonded propyl chloride (CBPC)

Cellulose (10.0 g) was suspended in dry toluene (100 mL) and then 3-chloropropyl trimethoxy silane (10.0 mL) was added followed by triethyl amine (1 mL) as a catalyst. The suspension was mechanically stirred as it was heated under reflux for 32 h. The reaction was cooled to room temperature and the crystalline product was isolated by filtration. The collected powder was washed for 12 h in a soxhlet extractor using 2-propanol as a solvent and was dried under vacuum at 80 °C for 4 h to give cellulose bonded N-propylchlorid.

Preparation of cellulose bonded N-propyldiethylenetriamine (CBPDETA)

To a mixture of cellulose bonded N-propylchlorid (10 g) in dry toluene (100 mL), diethylenetriamine (10 mL) was added and the mixture was heated under reflux with stirring for 24 h. The reaction was cooled to room temperature and the crystalline product was isolated by filtration. The collected powder was washed for 12 h in a soxhlet extractor using toluene as a solvent. The product was dried under vacuum overnight at 80 °C to give CBPDETA.

Preparation of cellulose bonded N-propyl diethylene tetrasulfamic acid (CBPDETSA)

To a magnetically stirred mixture of CBPDETA (5 g) in CH_2Cl_2 (20 ml) at 0 °C, chlorosulfonic acid (2.00 g, 18 mmol) was added dropwise over 1 h. After the addition was complete, the mixture was stirred for 4 h until all HCl was removed from the reaction vessel. The mixture was filtered, washed with methanol and diethyl ether (30 ml) and then dried at room temperature to give CBPDETSA as a white powder.

General procedure for the synthesis of tetrahydrobenzo [a]xanthenes-11-one

A mixture of 2-naphthol (1 mmol), aldehyde (1 mmol), 1,3-diketone (1 mmol), CBPDETSA (0.15 mmol) was heated at 110 ^{o}C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in acetone and was filtered to recover the catalyst. The filtrate was evaporated and the crude product was recrystallized from iso-propanol to afford the pure tetrahydrobenzo[a] xanthenes- 11-one derivatives in 70–92% yields.

Selected data 12-(4-methylphenyl)-5,8,9,10,12,12a hexahydro-11H-benzo[a]xanthen-11one (Table 3, Compound 10)

White Solid; mp= 202 ^{o}C, IR (KBr, v_{max}, cm^{-1}) 3050, 3030, 2940,2880, 1640, 1610, 1590, 1500, 1450, 1400, 1370, 1220, 1176, 1136, 1108, 1018, 1005. ^{1}H-NMR ($CDCl_3$, 250MHz): δ 1.75-1.95 (m, 3H), 2.12 (s, 3H), 2.25-2.71 (m, 3H), 5.53 (s, 1H), 6.90 (d, J= 8.4 Hz, 2H), 7.40- 7.35 (m, 6H), 7.95 (t, J= 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 62.9MHz): δ 20.4, 20.9, 27.3, 34.1, 36.9, 115.0, 117.5, 117.8, 123.7, 125.4, 127.5, 128.4, 129.0, 129.2, 129.4, 131.0, 131.5, 135.7, 142.7, 147.5, 166, 196.6, MS: m/z(%) 341 (2, M+1), 340 (9, M^{+}), 325 (1), 268 (4), 249 (100), 221 (3), 193 (6), 178 (6), 164 (35), 152 (14), 91 (19), 77 (8).

12-(4-metoxyphenyl)-9,9-dimethyl-5,8,9,10,12,12a-hexahydro-11H-benzo[a] xanthen- 11one (Table 3, Compound 19)

White Solid. mp= 220 ^{o}C. IR (KBr, v_{max}, cm^{-1}): 3057, 3020, 2985, 2920, 2875, 1640, 1617, 1592, 1510, 1457, 1395, 1362, 1210. 1162, 1132, 1115, 1035 ^{1}HNMR (250MHz, DMSO) δ: 0.88 (s, 3H), 1.04 (s, 3H), 2.09-2.64 (m, 4H), 3.60 (s, 3H), 5.47 (s, 1H), 6.70 (d, J= 8.4 Hz, 2H), 7.43- 7.85 (m, 6H), 8.0 (t, J= 8.7 Hz, 2H). ^{13}CNMR (62.9 MHz, DMSO) δ: 26.8, 27.1, 29.3 , 32.5, 33.7, 50.7, 55.4, 113.8, 117.8, 118.4, 123.9, 125.5, 127.7, 127.9, 128.8,129.5, 129.7, 131.4, 131.4, 137.2, 146.7, 157.6, 164.2, 196.5, MS: m/z (%) 385 (6, M+1), 384 (18, M^{+}), 299 (7), 281 (9), 277 (98), 257 (27), 227 (37), 164 (94), 144 (80), 89 (52), 76 (100).

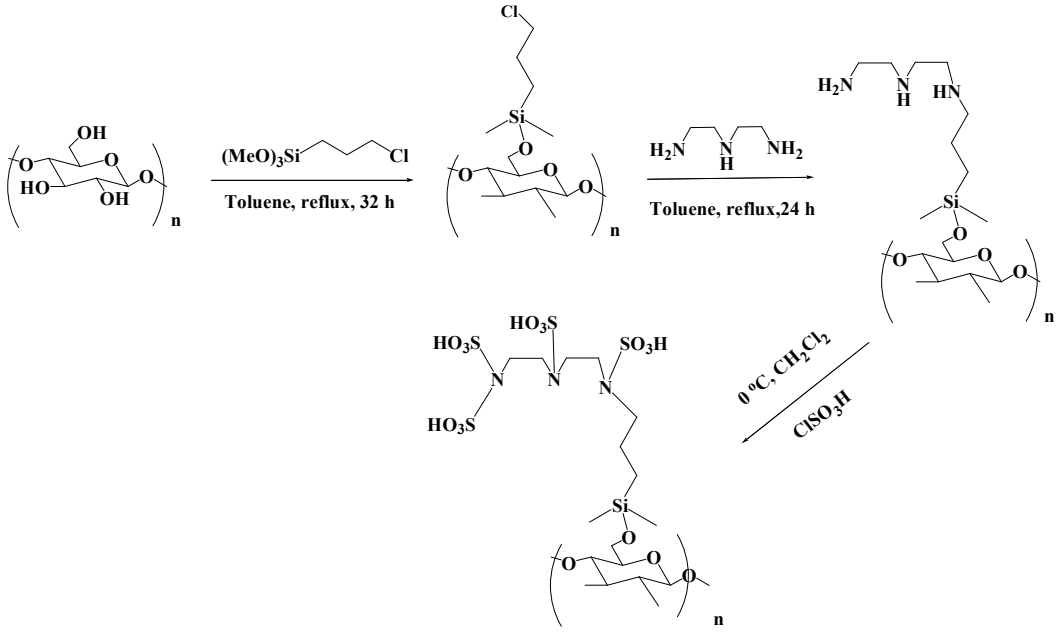
12-(4- chlorophenyl)- 9,9-dimethyl-5,8,9,10,12,12a hexahydro-11H benzo[a] xanthen- 11 one (Table 3, Compound 20)

Yellow Solid. mp= 219 ^{o}C. IR (KBr, v_{max}, cm^{-1}) 3065, 3005, 2940, 2880, 2860, 1645, 1615, 1595, 1511, 1480, 1400, 1360, 1330, 1250, 1220, 1175, 1084, 1004, 830, 804, 748, 670. ^{1}HNMR (250MHz, $CDCl_3$) δ: 0.96 (s, 3H), 1.12 (s, 3H), 2.27 (s, 2H), 2.56 (s, 2H), 5.69 (s, 1H), 6.32 (d, J= 8.4 Hz, 2H), 7.42-7.75 (m, 6H), 7.90 (t, J= 8.7 Hz, 2H).

^{13}CNMR (62.9MHz, $CDCl_3$) δ: δ 27.1, 27.5, 29.3, 32.2, 34.2, 41.4, 50.8, 113.8, 117.3, 123.4, 125.0, 127.1, 128.4, 129.1, 129.8, 131.2, 131.5, 131.9, 143.2, 147.7, 164.0, 196.8. MS: m/z (%) 390 (6, M+2), 388 (4, M+1), 388 (12, M^+), 331 (2), 317 (3), 304 (2), 277 (100), 239 (6), 221 (13), 193 (12), 164 (28), 139 (6), 76 (4).

Results and discussion

Due to the reasonable needs to clean, green and recyclable heterogeneous catalyst, we synthesized cellulose bonded N-propyl diethylene tetrasulfamic acid (CBPDETSA) as a new heterogeneous system. Firstly, cellulose propyl chloride was prepared by the reaction of cellulose with (3-chloropropyl) trimethoxy silane in dry toluene for 32 h. Then resulting compound was treated with diethylene triamine in dry toluene for 24 h to give cellulose bonded *N*-propyl diethylene triamine (CBPDETA). The reaction of CBPDETA with chlorosulfonic acid gave cellulose bonded N-propyl diethylene tetrasulfamic acid (CBPDETSA) (Scheme 2). Elemental analysis gave the following results: C, H, N and S 24.02 %, 5.0 %, 0.78 and 2.33 %, respectively. Ratio N:S determined from elemental analysis 3:4 was obtained. The number of H^+ sites of CBPDETSA was also determined by acid-basic titration and found to be 0.8 mmol H^+ sites per 1 g of solid acid. The content of S obtained from elemental analysis showed that typically a loading of 0.72 mmol/g H^+ was obtained.



Scheme 2. Preparation of cellulose bonded *N*-propyl diethylene tetrasulfamic acid (CBPDETSA).

Table 1. Effect of solvents on the model reaction catalyzed by CBPDETSA[a]

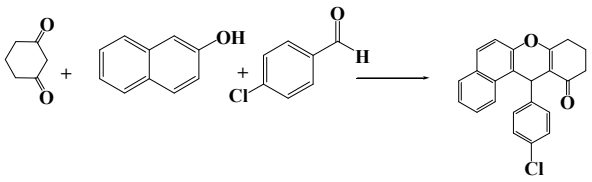
So.nu	Solvent	Time (h)	Yield (%)[b]
1	n-Hexane	12	12
2	CH_2Cl_2	12	25
3	$CHCl_3$	12	18
4	$ClCH_2CH_2Cl$	12	27
5	THF	12	30
6	DMF	10	35
7	DMSO	10	33
8	CH_3CN	10	56
9	EtOAc	8	72
10	EtOH	8	75
11	MeOH	7	78
12	H_2O	7	75
13	Ethylen Glycol	2	83
14	Solvent-Free,80 ^oC	0.5	78

[a]The reactions were run under reflux condition, and the molar ratio of 4-chloro benzaldehyd/ 1,3- cyclohexadione / 2- naphtol / catalyst was 1: 1: 1: 0.1 mmol.
[b]Yields are related to isolated pure products.

In order to show the merit of synthesized heterogeneous catalyst in organic reactions, CBPDETSA was used as an efficient and inexpensive heterogeneous catalyst for synthesis of synthesis of tetrahydrobenzo [a] xanthenes-11-one by the coupling of 2-naphtol, cyclohexadione and aldehyde derivatives. In an initial endeavor, 1,3-cyclohexadione, 4-chloro benzaldehyde and 2-naphtol were selected as the model substrates and reacted under different experimental variants (Scheme 3).

We examined the reaction under different conditions including refluxing in various solvents. In refluxing of solvents, the yield of products was low (Table 1). To

improve the yield reaction conditions, the same reaction was carried out under solvent-free conditions that a significant improvement was observed and the yield of benzoxanthene was increased to 78%.



Scheme 3. Synthesis of 12-(4-chlorophenyl)-5,8,9,10,12,12a hexahydro-11H-benzo[a]xanthen-11one

To obtain the optimized reaction conditions, we also changed temperature and the amount of catalyst. The results are summarized in Table 2. Consequently, among the tested temperature and the amount of catalyst, the condensation of 1,3-cyclohexadione, 2- naphtol and 4-chlorobenzaldehyde was best catalyzed by 0.1 mmol of CBPDETSA at 100 ^{o}C as the reaction was completed within high yield. To establish the catalytic role of CBPDETSA, 1,3- cyclohexadione and 2-naphtol was treated with 4-chlorobenzaldehyde in the absence of catalyst. In this case, the reaction did not proceed under reflux and solvent free conditions in low yield over model reaction times. Although the coupling of 1,3-cyclohexadione, 2-naphtol with 4-chlorobenzaldehyde was successful in the presence of catalytic amounts of CBPDETSA (10 mol%).

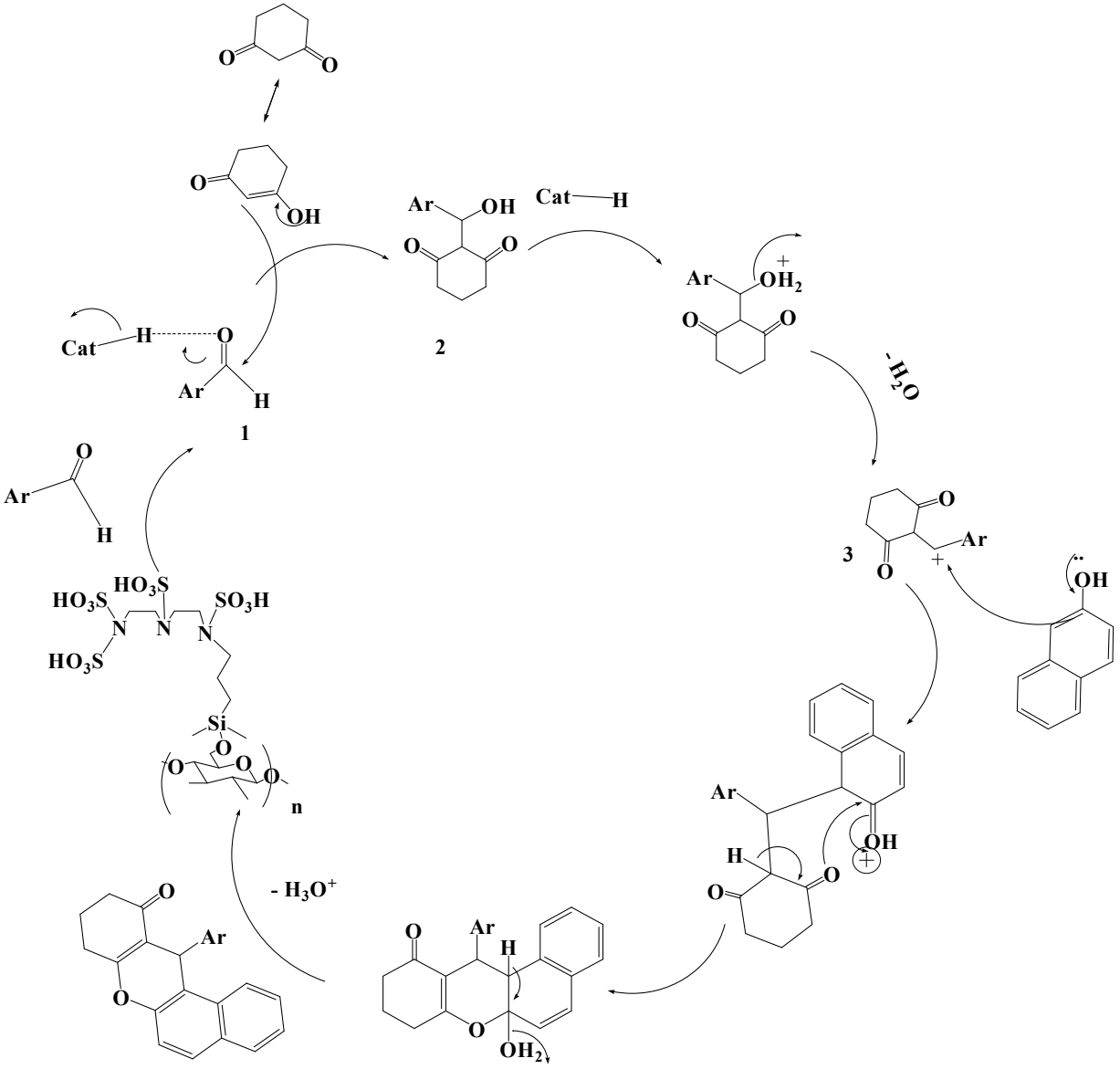
To ascertain the scope and limitation of the present reaction, with optimized conditions in hand, variety of aromatic aldehydes was examined and these results were summarized in Table 3. We were pleased to find that all substrates were converted to the corresponding products in good to excellent yields (70-92%).

Table 2 . Effect of temperature and the amount catalyst on model reaction in the presence of CBPDETSA

Entry	Catalyst (mmol)	Yield%			
		r.t	60^0C	80^0C	100^0C
1	0.01	15	20	28	45
2	0.05	28	42	55	68
3	0.1	42	56	78	92
4	0.2	55	68	82	95
5	None	-	-	12	25

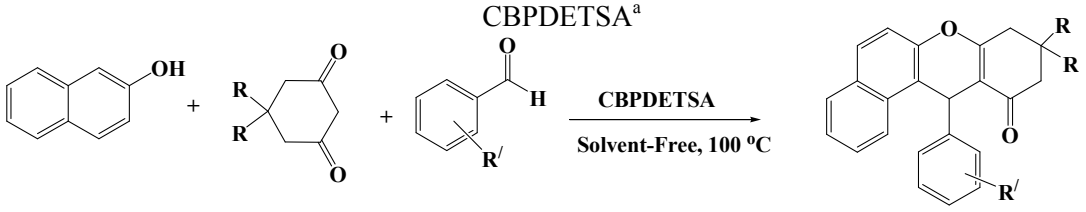
[a]The reactions were run under solvent- free condition, and the molar ratio of 1,3-cyclohexadione/ 4-chlorobenzaldehyde and 2-naphtol was 1:1:1 for 30 min.
[b]Isolated yields

In all cases, the obtained product was isolated by a simple filtration, washed with water and purified by recrystallization from ethanol or 2 propanol. The reactivity of different aromatic aldehydes was influenced by the nature and position of the substituents on the aromatic ring. The benzaldehyde derivatives having an electron-withdrawing substituent were highly reactive and gave the products in excellent yields.



Scheme 4. The proposed mechanism for the synthesis of tetrahydrobenzo[a]xanthenes-11-one in the presence of CBPDETSA

Table 3. Solvent-free synthesis of tetrahydrobenzo[a]xanthenes-11-one in the presence of CBPDETSA[a]



Entry	R	R/	Time(min)	Yield(%)[b]
1	H	H	30	83
2	H	2-NO_2	20	85
3	H	3-NO_2	20	88
4	H	4-NO_2	20	92
5	H	2-Cl	20	78
6	H	3-Cl	20	83
7	H	4-Cl	20	88
8	H	2-CH_3	35	70
9	H	3-CH_3	35	72
10	H	4-CH_3	35	76
11	H	2-CH_3O	45	78
12	H	3-CH_3O	45	78
13	H	4-CH_3O	45	82
14	Me	2-NO_2	20	88
15	Me	3-NO_2	20	92
16	Me	4-NO_2	20	95
17	Me	2-CH_3O	45	82
18	Me	3-CH_3O	45	82
19	Me	4-CH_3O	45	88
20	Me	4-Cl	20	90

[a]Reaction condition: 2-naphtol (1 mmol), cyclohexadione (1 mmol), aldehyde (1 mmol), CBPDETSA (0.1 mmol) at 100 ^oC

[b]The yield refers to pure isolated product.

Based on the experimental results, a plausible mechanism was proposed in Scheme 4. In this hypothesis, CBPDETSA might be served as the bronsted-acid catalyst for several stages.The first step involves the formation of activated aldehyde (1) followed by its reaction with 1,3-cyclohexadione to generate compound 2 that subsequently undergoes elimination reaction to produce the compound 3. Intermediate 3 undergoes further addition with 2-naphtol molecule to afford xanthene derivatives.

At the end of the reaction, the catalyst could be recovered by filtration. The recycled

catalyst was washed with dichloromethane and subjected to a second reaction process. The results show that the yield of product after five runs was only slightly reduced (Table 4).

Table 4. Recyclability of CBPDETSA as a catalyst in model reaction[a]

Entry	Cycle	Yield (%)[b]
1	0	88
2	1	88
3	2	88
4	3	86
5	4	86
6	5	82

[a]Reaction condition: 2-naphtol (1 mmol), 1,3-cyclohexadione (1 mmol), 4- chlorobenzaldehyde (1 mmol), CBPDETSA (0.1 mmol) for 20 min.

[b]The yield refers to pure isolated product.

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