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Diethylenetriamine supported on cellulose as a biodegradable and recyclable basic heterogeneous catalyst for the synthesis of spirooxindole derivatives

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ABSTRACT

In the present study, the synthesis of diethylene triamine supported on cellulose biopolymer as a biodegradable solid basic heterogeneous catalyst was suggested. Then, the applicability of the synthesized catalyst cellulose bonded N-propyl diethylene triamine (CBPDETA) was tested for the synthesis of oxindole derivatives, an important class of potentially bioactive compounds. A various series of tetrahydrospiro-[chromene-indoline]-carbonitrile and dihydro-spiro[pyrano quinoline--indoline]-carbonitrile are obtained in water, an excellent solvent in terms of environmental impact, in high yield (78- 98%) from one-pot reaction procedure involving dicarbonyl/4-hydroxycoumarine, malononitrile and isatin compounds. The catalyst has been reused several times, without observable loss of activity and selectivity.

***Keywords**: Heterogeneous Catalyst; Cellulose; CBPDETA; Oxindole.*

1. Introduction

Heterogeneous catalysts for the synthesis of fine chemicals have attracted considerable interest from both environmental and economical points [1, 2]. One of the recent investigated methods which could conform to standards of green chemistry is eco-friendly, natural product resources and reusable catalysts [3]. In this regard, natural biopolymers are attractive candidates in the search for support catalysts. Biopolymers such as alginate, gelatin, starch and chistosan derivatives have been used as support for catalytic applications, [4-8] but cellulose has some properties which make it unique for conventional organic or inorganic in catalytic applications. Cellulose is the most abundant natural marital in the world, biodegradable substrate and a renewable resource [9]. On the other hands, heterogeneous acid catalysts have been extensively studied and applied in numerous reactions so far; however, heterogeneous base catalysts have not been extensively studied [10-12]. The potential use of microporous and mesoporous base catalysts in fine chemical production is enormous [13]. These heterogeneous catalysts are known to suppress side reactions, which include better selectivity and product yield. This means cost and energy savings for the downstream separation and purification of the product. It also avoids the complex neutralization and separation steps needed to recover the homogeneous base catalysts from the reaction mixture.

The recovered solid catalysts can be readily regenerated for further use. On a different note, indoline and oxindole which are important fragments of a large number of natural products and medicinal agents have shown good biological activity [14-19]. Oxindoles are known to possess antibacterial, antiprotozoal and anti-inflammatory activities and are also patented as PR (progesterone receptors) agonists [20, 21]. Among the oxygen-containing heterocycles fused with spirooxindole ring system, chromenes are of particular utility as they belong to 'privileged medicinal scaffolds'—certain molecular frameworks serving for the generation of ligands for functionally and structurally discreet biological receptors [22]. Functionally substituted 4H-chromenes have received considerable attention due to their wide range of useful biological properties, which include spasmolitic, diuretic, anticoagulant, anticancer, and antianaphylactic activities [23]. There are several reports on multicomponent entries to the synthesis of spirooxindoles.

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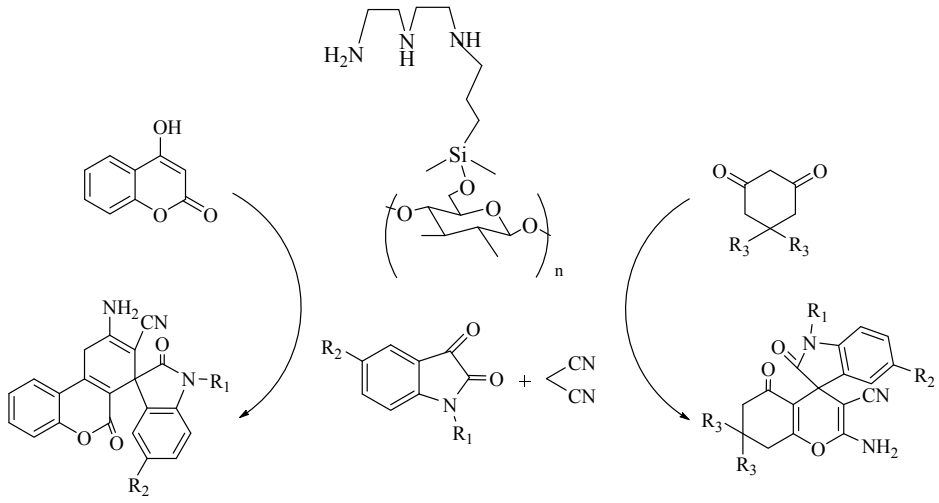


Scheme 1. Synthesis of spiro oxindoles.

Recently, Shanthi et al. reported a three-component condensation of cyclic 1,3-diketones, isatin, and malononitrile catalyzed by 20 mol % of $InCl_3$ [24]. Spirooxindoles were also prepared by electrochemical methods [25] that suffer from technical intricacy. This reaction was carried out in the presence of the surfactant triethylbenzylammonium chloride (TEBA) in water medium [26].

An important disadvantage of this approach was the generation of mixtures of pyrans and unsaturated nitriles. Therefore, the development of new synthetic methods for the efficient preparation of heterocycles containing oxindole fragment is an interesting challenge. In the present study, for the first time, we prepared cellulose bonded N-propyl diethylenetriamine (CBPDETA) and studied its catalytic activity in the synthesis of tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile and dihydro-spiro [pyrano [3,2c] quinoline - 4,3' - indoline] -3-carbonitrile by the coupling of malononitrile, 1,3-dicarbonyl/4-hydroxycoumarine and isatin derivatives (Scheme 1).

2. Experimental

2.1. General

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}HNMR and ^{13}CNMR 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.

2.2. Preparation of cellulose bonded propyl chloride (CBPC)

10.0 g Cellulose (pH=5) 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.

2.3. 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 (pH=8).

2.4. General procedure for the preparation of oxindol derivatives

A mixture of malononitrile (1 mmol), isatin (1 mmol), dicarbonyl (1 mmol), CBPDETA (0.05 gr) and water (2 mL) was stirred under ambient condition for the appropriate time, as shown in Tables 3 and 4. Completion of the reaction was indicated by TLC monitoring. After completion of the reaction, the reaction mixture was dissolved in acetone and catalyst was isolated by filtration. The product was afforded by evaporation of solvent and was recrystallized from

EtOH to afford the pure products in high purity and yield.

Selected spectral data

Table 3, entry 1:

White solid. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 1.91 (2H, m), 2.10 (2H, m), 2.62 (2H, m), 6.68 (d,1H, *J*= 7.4 Hz), 6.88 (t, 1H, *J*= 7.4 Hz), 7.10 (d, 1H, *J*= 7.4 Hz), 7.22 (t, 1H, *J*= 7.4 Hz), 7.35 (s, 2H), 10.65 (s, 1H) ppm. ^{13}CNMR (62.9MHz, DMSO-d_6): δ= 195.1, 178.2, 166.1, 158.7, 142.0, 134.6, 128.5, 123.3, 121.8, 117.4, 111.9, 109.2, 57.6, 46.9, 36.4, 26.8, 19.8 ppm. IR (KBr): $\bar{\nu}$ = 3352, 3296, 3176, 2952, 2204, 1712, 1656, 1352, 1216, 1076 cm^{-1}. Found: C, 66.38; H, 4.32; N, 13.74% $C_{17}H_{13}N_3O_3$; requires: C, 66.44; H, 4.26; N, 13.67%.

Table 3, entry 2:

White solid. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 1.00 (3H, s), 1.1 (3H, s), 2.08-2.19 (2H, m), 2.56 (2H, m), 6.70 (d,1H, *J*= 7.4 Hz), 6.88 (t, 1H, *J*= 7.4 Hz), 7.10 (d, 1H, *J*= 7.4 Hz), 7.22 (t, 1H, *J*= 7.4 Hz), 7.35 (s, 2H), 10.65 (s, 1H) ppm.^{13}CNMR (62.9 MHz, DMSO-d_6): δ= 195.3, 178.5, 166.58, 159.20, 152.4, 142.48, 134.83, 128.59, 123.4, 122.16, 117.76, 111.22, 109.7, 57.96, 50.45, 47.23, 32.35, 28.01, 27.1 ppm. IR (KBr): $\bar{\nu}$ = 3376, 3312, 3144, 2928, 2196, 1724, 1656, 1348, 1224, 1056 cm^{-1}. Found: C, 67.94; H, 5.15; N, 12.64% $C_{19}H_{17}N_3O_3$; requires: C, 68.05; H, 5.11; N,12.53%.

Table 4, entry 1:

White solid. ^{1}HNMR (250 MHz, DMSO-d_6): δ= 6.83 (1H, d, *J*= 7.6 Hz), 6.92 (1H, t, *J*= 7 7.6 Hz), 7.17 (1H, d, *J*= 7.2 Hz), 7.32 (1H, d, *J*= 7.6 Hz), 7.44 (1H, t, *J*= 7.6 Hz), 7.48 (1H, t, *J*= 8.2 Hz), 7.52 (1H, d, *J*= 8.4 Hz), 7.53 (2H, s), 7.95 (1H, d, *J*= 8.2 Hz), 10.65 (1H, s) ppm. ^{13}CNMR (62.9MHz, DMSO-d_6) 177.4, 158.9, 155.7, 155.5, 152.4, 142.6, 134.1, 133.5, 129.38, 125.4, 124.5, 123.12, 122.52, 117.42, 117.09, 112.9, 109.9, 101.9, 70.2, 57.5 ppm. IR (KBr): $\bar{\nu}$ = 3415, 3241, 3260, 2218, 1719, 1679, 1623, 1581 cm^{-1}; Found: C, 67.35; H, 3.12; N, 11.64% $C_{20}H_{11}N_3O_4$; requires: C, 67.23; H, 3.10; N,11.76%.

3. Results and Discussion

Initially, we synthesized cellulose bonded N-propyl diethylene triamine as a new heterogeneous system. 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 for 24 h to give cellulose -bonded N-propyl diethylene triamine (Scheme 2). Elemental analysis gave the following results: C, H, and N, 40.55%, 5.45%, and 1.78%, respectively. The content of NH_2 obtained from elemental analysis showed that typically a loading of 1.2 mmol/g NH_2 was obtained. The number of NH_2 sites of CBPDETA was also determined by acid- basic titration and found to be 1.1 mmol basic sites per 1 g of catalyst.

Fig. 1 shows the IR spectrum of CBPDETA. The peaks at 3415 and 1120 cm^{-1} appear which are assigned to the –OH and C-O group, respectively. CH_2 bending at 1480 cm^{-1} and C–C stretching at 1050 cm^{-1} are observed. The IR spectrum shows an overlap of the stretching bands of OH with the NH_2 stretching bands in CBPDETA.

In order to show the merit of synthesized heterogeneous catalyst in organic reactions, CBPDETA was used, for the first time, as an efficient and inexpensive heterogeneous catalyst for synthesis of oxindoles.

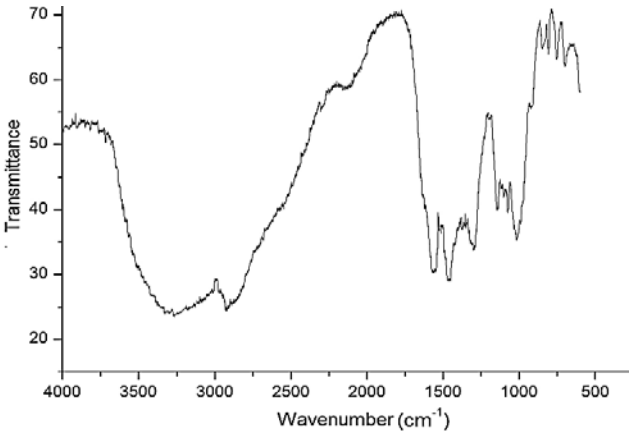
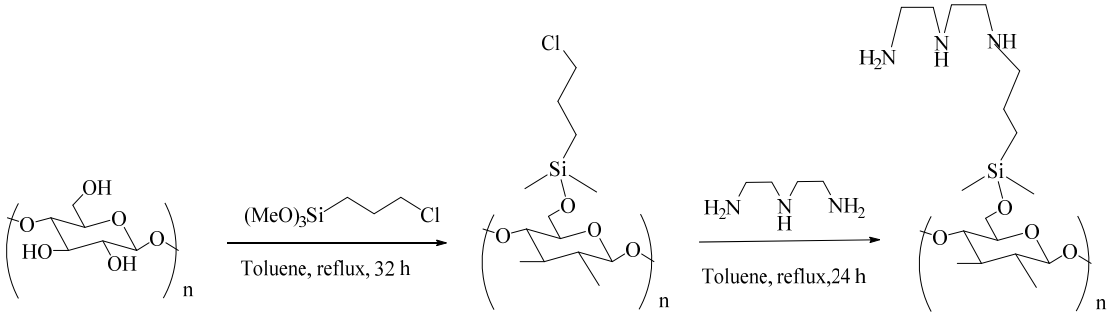
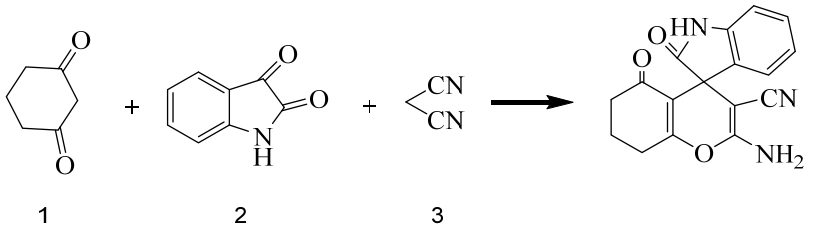


Fig. 1. IR spectrum of CBPDETA



Scheme 2. Preparation of Cellulose -Bonded *N*-Propyl Diethylenetriamine (CBPDETA).



1 2 3

Scheme 3. Synthesis of 2-Amino-2',5-dioxo-5,6,7,8-tetrahydro spiro-[chromene- 4,3'- indoline]-3-carbonitrile.

Initially, 1,3-cyclohexadione (1), isatin (2) and malononitrile (3) were selected as the model substrates (Scheme 3) and reacted in various solvents under ambient condition. The reaction proceeded perfectly in polar solvents (Table 1, entries 1-6), but the yields decreased when the reaction was carried out in non-polar solvents (Table 1, entries 7-10). The reaction carried out under solvent-free conditions and gave low yield (Table 1, entry 11). It was very surprising that the model reaction proceeded in excellent yields (98%) in short time (5 min) in aqueous medium (Table 1, entry 1).

To evaluate catalytic activity of CBPDETA, the model reaction was carried out in water (2 mL) under ambient condition for 5 min in the presence of different catalytic systems, separately. The results are shown in Table 2. As it is evident from the results, 0.05 gr of CBPDETA was the most effective catalyst in terms of yield of the oxindole (98%) while other catalysts(0.1 gr) formed the product with the yields of 25- 35 % (Table 2, Entries 1-7).

To illustrate the need of CBPDETA for this condensation we examined the model reaction in the absence of catalyst. In this case, the reaction gives oxindole in a rather low yield (Table 2, entry 13). Obviously, CBPDETA is an important component of the reaction. The optimal amount of CBPDETA was 0.05 g per one mmol of reagents in water at room temperature. To further explore the scope and limitation of this protocol particularly in regard to library construction under the optimized conditions (0.05 gr catalyst in H_2O at r.t), this reaction was evaluated using various isatin and 1,3-dicarbonyl compounds (Scheme 4, Table 3).

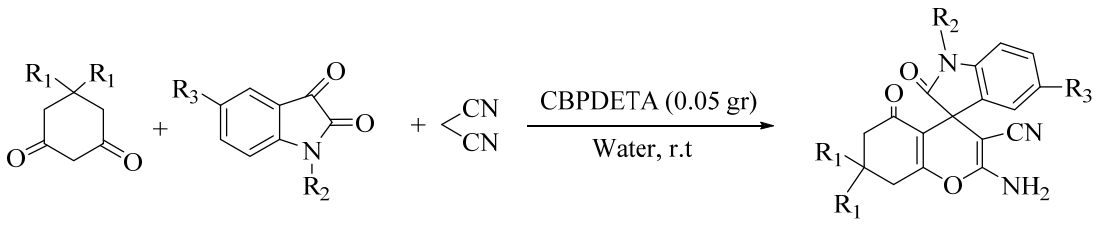
In all cases, the reaction proceeded readily to afford the corresponding oxindoles in high to excellent yields (78- 98%) in very short reaction times (5– 20 min). It is delighted that the reaction time of isatin was longer than those of electron-withdrawing substituents, which is probably due to more reactivity of carbonyl groups by electron-withdrawing groups (Table 3, entries 1-6). The reaction of dicarbonyl compounds with N-methyl/ N-ethyl isatin in the presence of CBPDETA proceeded well giving the crosspending product in excellent yields without formation of by product (Table 3, Entries 7-10), however, the reaction of dicarbonyls with N-benzylisatin required longer reaction times and producing the adducts in lower yields (Table 3, Entries 11, 12).

The reaction of dimedone took place faster than 1,3-cyclohexadione analogues that this behavior could result from the more reactivity of dimedone by electron-donating groups (Me). These reactions also proceeded with 4-hydroxy coumarine (Table 4). In these cases, the reaction times are longer than 1,3-diketones. It may be due to the less activity of 4-hydroxy coumarine than dicarbonyl compounds. It is noteworthy to mention that the catalyst is recyclable and could be reused without significant loss of activity. At the end of the reaction, the catalyst could be recovered by filtration.

The recycled catalyst was washed with diethyl ether and was subjected to another reaction. In the model reaction the results of the first experiment and the subsequent were almost consistent in yield after 5 runs(Table 5).

4. Conclusions

In summary, a safe, environment-compatible protocol for the preparation of spirocyclic(5,6,7,8-tetrahydro-4H-chromene)-4,3'-oxindole and tetrahydro[pyrano [3,2-c]quinoline]-4,3-indoline derivatives in water using CBPDETA as a green basic catalyst was described.



Scheme 4. Synthesis of tetrahydro spiro- chromene indoline.

Table 1. Effect of solvents on the synthesis of oxindole catalyzed by CBPDETA[a].

Entry	Solvent	Time (min)	Yield (%)[b]
1	H_2O	5	98
2	EtOH	50	95
3	MeOH	5	95
4	EtOAc	15	91
5	DMSO	15	88
6	DMF	20	85
7	$ClCH_2CH_2Cl$	35	58
8	THF	50	55
9	$CHCl_3$	60	46
10	CH_2Cl_2	60	45
11	Solvent-free	60	42

[a]Reaction conditions: reagents (1 mmol), catalyst (0.05 gr), solvent (2 mL) in r.t.
[b]Isolated yields.

Table 2 One-pot three-component synthesis of oxindole in the presence of various catalytic systems[a].

Entry	Catalyst (gr)	Yield (%)[b]
1	SiO_2 (0.1)	25
2	Acidic Al_2O_3 (0.1)	28
3	Basic Al_2O_3 (0.1)	25
4	Cellulose (0.01)	18
5	Cellulose (0.05)	20
6	Cellulose (0.1)	35
7	Cellulose (0.5)	68
8	CBPDETA (0.01)	28
9	CBPDETA (0.02)	45
10	CBPDETA (0.05)	98
11	CBPDETA (0.1)	98
12	CBPDETA (0.2)	98
13	None	15

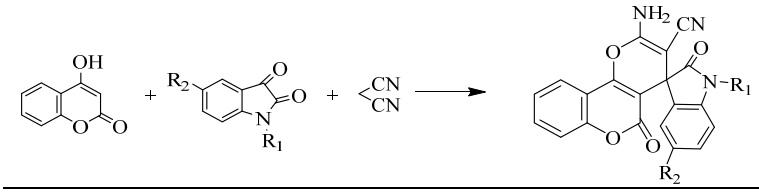
[a]1,3-dicarbonyl compounds (1 mmol), isatin (1 mmol), malononitrile (1 mmol) and H_2O (2 mL) stirred at r.t. for 5 min.
[b]Isolated yields.

Table 3. Preparation of oxindole derivatives[a].

Entry	Reactant			Time (min)	Yield (%)	m.p.(°C)
	Dicarbonyl	Isatin				
	R_1	R_2	R_3			
1	H	H	H	5	98	251-253
2	Me	H	H	5	90	289-290
3	H	H	Br	7	89	289-292
4	Me	H	Br	5	91	292-293
5	H	H	NO_2	5	95	278-279
6	Me	H	NO_2	5	93	282-283
7	H	Et	H	10	85	242-244
8	Me	Et	H	10	88	253-254
9	H	Me	H	10	82	240-241
10	Me	Me	H	15	85	250-252
11	H	$PhCH_2$	H	20	78	283-284
12	Me	$PhCH_2$	H	20	80	295-297

[a]Reaction conditions: dicarbonyl compounds (1 mmol), isatins (1 mmol), malononitrile(1 mmol), catalyst (0.05 gr), and H_2O (2 mL) at r.t.
[b]Isolated yields.

Table 4. Preparation of indoline derivatives[a].



Entry	Reactant		Time (min)	Yield (%)
	R_1	R_2		
1	H	H	10	90
2	H	Br	10	95
3	H	NO_2	15	95
4	H	Me	15	88
5	Me	H	10	87
6	Et	H	10	85
7	Et	NO_2	15	92
8	Me	NO_2	15	94
9	$PhCH_2$	H	15	84
10	$PhCH_2$	Br	15	87

[a]Reaction conditions: 4-hydroxy coumarine (1.0 mmol), isatin (1.0 mmol), malononitrile (1.0 mmol), catalyst (0.05 gr), and H_2O (2 mL) at r.t.
[b]Isolated yields.

Table 5 Recyclability of CBPDETA as a catalyst in synthesis of oxindoles[a].

Cycle	0	1	2	3	4	5
Yield (%)[b]	98	98	96	95	93	91

[a]Reaction conditions: 1,3-cyclohexadion compounds (1 mmol), isatin (1 mmol), malononitrile (1 mmol) and H_2O (2 mL) stirred for 5 min at r.t.
[b]The yield refers to pure isolated product.

The procedure offers several advantages including the cheapness and the availability of the catalyst, mild reaction conditions and high yields of the products as well as simple experimental and isolation procedures that make this protocol a useful and an attractive procedure for the synthesis of oxindole derivatives.

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