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Sulfuric acid-modified poly(ethylene glycol): an efficient, biodegradable, and reusable polymeric catalyst for synthesis of spiro oxindole derivatives in aqueous medium

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Abstract A versatile, novel, and environmentally benign strategy has been successfully developed for synthesis of oxindoles, an important class of potentially bioactive compounds. Sulfonated poly(ethylene glycol) was used as inexpensive and recyclable acidic catalyst. The products were obtained in water, an excellent solvent in terms of environmental impact, in high yield, by one-pot reaction of malononitrile, 1,3-dicarbonylcoumarin or 4-hydroxycoumarin derivatives, and isatins. This new method totally avoids the use of organic acids and toxic or expensive solvents.

Keywords PEG-OSO_3H · Spirooxindole · Indoline · 4-Hydroxycoumarin · Isatins

Introduction

Recent use of solid acidic catalysts as safer alternatives to mineral acids has important advantages in organic synthesis, for example operational simplicity, environmental compatibility, lack of toxicity, reusability, low cost, and ease of isolation [1, 2]. Recently, soluble polymeric supports have been envisaged as possible alternatives to their insoluble counterparts for catalyst immobilization, Because they would secure higher chemical and stereochemical efficiency than insoluble polymers. Poly(ethylene glycols) (PEGs) are highly favorable soluble polymeric matrixes, and PEGs with molecular weight >2,000 Da have extensively been used as inexpensive and easily functionalized supports for immobilization of catalysts. PEGs are readily soluble in water and polar organic solvents (e.g.,

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dichloromethane, acetonitrile, DMF, DMSO) and insoluble in less polar solvents (e.g., *n*-hexane, diethyl ether, *tert*-butyl methyl ether). Because of this solubility profile, PEG-based supports combine high reactivity and analytical simplicity (advantageous features of homogeneous solution chemistry) with ready isolation and purification of products (advantageous features of solid-phase methods). Poly(ethylene glycol)-bound sulfonic acid (PEG-OSO_3H) is an interesting example of PEG-supported catalysts that has emerged as an efficient Brønsted acid for promotion of a variety of organic transformation, for example the synthesis of 3,4-dihydro pyrimidones [3], quinolines [4, 5], α-amino phosphonates [6], β-amino carbonyls [7], and acetamido carbonyls [8].

The indoline and oxindole structures are important components of a large number of natural products and medicinal agents with good biological activity [9–18]. Oxindoles are known to have antibacterial, antiprotozoal, and anti-inflammatory activity and are also patented as PR (progesterone receptor) agonists [19, 20]. Among oxygen-containing heterocycles fused to the spirooxindole ring system, chromenes are of particular utility, because they are "privileged medicinal scaffolds"—molecular frameworks serving for the generation of ligands for functionally and structurally discreet biological receptors. Functionally substituted 4*H*-chromenes have attracted much attention because of their wide range of useful biological properties, which include spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activity [21, 22].

Organic solvents, which are used in huge amounts for many different applications, have a negative impact on health and the environment. An important aspect of green chemistry is elimination of solvents from chemical processes or replacement of hazardous solvents with environmentally benign solvents. Water has emerged as a useful alternative solvent for several organic reactions, owing to its many advantages, for example safety and economy, and because it is environmentally benign. Sometimes it results in greater reactivity and selectivity than conventional organic solvents because of its strong hydrogen-bonding property [23, 24].

Because of the pharmacological properties of oxindoles, development of synthetic methods enabling easy access to these compounds are desirable. In this paper, we report the synthesis of spiro cyclic (5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindole and tetrahydro [pyrano [3,2-*c*]quinoline]-4,3-indoline derivatives by coupling of malononitrile, 1,3-dicarbonylcoumarin or 4-hydroxycoumarin derivatives, and isatins in the presence of sulfonated poly(ethylene glycol) in aqueous medium.

Experimental

Malononitrile, isatin, and 1,3-dicarbonylcoumarin and 4-hydroxycoumarin derivatives were purchased from Merck company. The purity of these compounds was determined by TLC on Polygram SILG/UV 254 silica gel plates. Melting points were measured by use of an Electrothermal 9100 apparatus. IR spectra were acquired on a Perkin Elmer 781 spectrometer, as KBr pellets, and are reported in

cm^{-1}. ^1H NMR and ^{13}C NMR spectra were acquired on a Bruker DPX-250 Avance instrument at 250 MHz and 62.9 MHz in $CDCl_3$ or DMSO-d_6; chemical shifts are given in ppm relative to TMS as internal standard.

Preparation of PEG-OSO_3H

Chlorosulfonic acid (1.16 g, 10 mmol) was added to a solution of PEG-6000 (6.0 g, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was stirred at room temperature overnight, then the solution was concentrated under vacuum. Diethyl ether (10 mL) was added to the concentrated solution, and the precipitate formed was isolated by filtration and washed with ether (3 × 30 mL) to afford PEG-OSO_3H [3].

General procedure for preparation of oxindole derivatives

A mixture of malononitrile (1 mmol), isatin (1 mmol), dicarbonyl (1 mmol), PEG-OSO_3H (0.1 mmol), and water (2 mL) was stirred under reflux for the appropriate time (shown in Tables 3, 4). After completion of the reaction, the reaction mixture was filtered and the residue was washed with ethanol. The crude solid product was recrystallized from EtOH to afforded the pure products in high purity and yield. Assignment of the structures of the products was based on their ^1H NMR, ^{13}C NMR, and IR spectra.

Selected spectral data

2-Amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro-[chromene-4,3′-indoline]-3-carbonitrile (Table 3, Compound 1)

White solid, mp >250 °C. ^1H NMR (250 MHz, DMSO-d_6) 1.91 (2H, m, CH_2), 2.10 (2H, m, CH_2), 2.62 (2H, m, CH_2), 6.68 (d, 1H, *J* 7.4 Hz, ArH), 6.88 (t, 1H, *J* 7.4 Hz, ArH), 7.10 (d, 1H, *J* 7.4 Hz, ArH), 7.22 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (s, 2H, NH_2), 10.65 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6) 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. IR (KBr, cm^{-1}) 3352, 3296, 3176, 2952, 2204, 1712, 1656, 1352, 1216, 1076. Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67 %. Found: C, 66.38; H, 4.32; N, 13.74 %.

2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3′-indoline]-3-carbonitrile (Table 3, Compound 6)

White solid, mp >250 °C. ^1H NMR (250 MHz, DMSO-d_6) 1.00 (3H, s, CH_3), 1.1 (3H, s, CH_3), 2.08–2.19 (2H, m, CH_2), 2.56 (2H, m, CH_2), 6.70 (d, 1H, *J* 7.4 Hz, ArH), 6.88 (t, 1H, *J* 7.4 Hz, ArH), 7.10 (d, 1H, *J* 7.4 Hz, ArH), 7.22 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (s, 2H, NH_2), 10.65 (s, 1H, NH) .^{13}C NMR (62.9 MHz, DMSO-d_6) 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. IR (KBr,

cm^{-1}): 3376, 3312, 3144, 2928, 2196, 1724, 1656, 1348, 1224, 1056 cm^{-1}. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53 %. Found: C, 67.94; H, 5.15; N, 12.64 %.

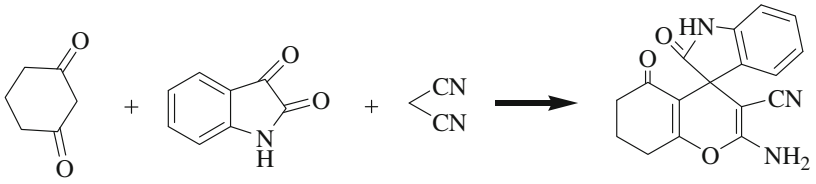
2-Amino-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile (Table 4, Compound 1)

White solid, mp >250 °C. 1H NMR (250 MHz, DMSO-d_6): 6.83 (1H, d, *J* 7.6 Hz, ArH), 6.92 (1H, t, *J* 7.6 Hz, ArH), 7.17 (1H, d, *J* 7.2 Hz, ArH), 7.32 (1H, d, *J* 7.6 Hz, ArH), 7.44 (1H, t, *J* 7.6 Hz, ArH), 7.48 (1H, t, *J* 8.2 Hz, ArH), 7.52 (1H, d, *J* 8.4 Hz, ArH), 7.53 (2H, s, NH_2), 7.95 (1H, d, *J* 8.2 Hz, ArH), 10.65 (1H, s, NH). ^{13}C NMR (62.9 MHz, 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. IR (KBr, cm^{-1}): 3415, 3241, 3260, 2218, 1719, 1679, 1623, 1581; Anal. Calcd for $C_{20}H_{11}N_3O_4$: C, 67.23; H, 3.10; N, 11.76 %. Found: C, 67.35; H, 3.12; N, 11.64 %.

Results and discussion

PEG-OSO_3H was prepared by anchoring chlorosulfonic acid on to poly(ethylene glycol) by use of a simple and convenient procedure. This polymeric catalyst was used as an efficient Brønsted acid catalyst for different organic functional group transformations either as reagent or as catalyst under heterogeneous and homogenous conditions. Initially, we focused on the synthesis of oxindoles from isatins and dicarbonyls. 1,3-Cyclohexadione (**1**), isatin (**2**), and malononitrile (**3**) were selected as model substrates and reacted under different experimental conditions (Scheme 1).

In preliminary experiment, this reaction was performed in different solvents, with PEG-OSO_3H (0.1 mmol) as a catalyst, under reflux conditions. The reaction proceeded perfectly in polar solvents (Table 1, entries 1–6), but yields decreased when the reaction was conducted in non-polar solvents (Table 1, entries 7–10). It was very surprising that the model reaction proceeded in excellent yields (98 %) in a short time (5 min) in aqueous medium (Table 1, entry 1). The reaction was performed under solvent-free conditions and gave a low yield (Table 1, entry 11).



Scheme 1 Synthesis of 2-amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro-[chromene-4,3′-indoline]-3-carbonitrile

Table 1 Effect of solvents on the synthesis of oxindole catalyzed by PEG-OSO_3H

Entry	Solvent	Time (min)	Yield (%)[a]
1	H_2O	5	98
2	EtOH	10	93
3	MeOH	10	91
4	EtOAc	20	89
5	DMSO	45	80
6	DMF	40	78
7	$ClCH_2CH_2Cl$	45	62
8	THF	60	60
9	$CHCl_3$	60	54
10	CH_2Cl_2	60	46
11	Solvent-free	60	35

Reaction conditions: reagents (1 mmol), catalyst (0.1 mmol), solvent (2 mL) under reflux conditions

[a] Isolated yields

Table 2 One-pot three-component synthesis of oxindole in the presence of different catalytic systems

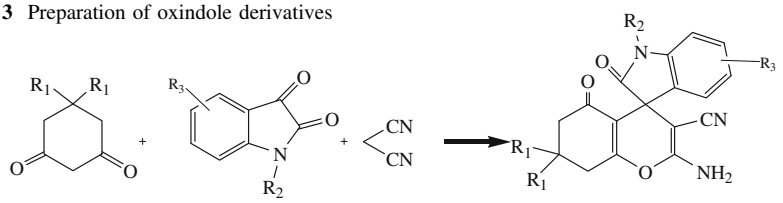
Entry	Catalyst (mol%)	Yield (%)[a]
1	SiO_2 (10)	20
2	Acidic Al_2O_3 (10)	18
3	Basic Al_2O_3 (10)	20
4	MgO (10)	15
5	CaO (10)	37
6	CdO (10)	45
7	$NbCl_5$ (10)	5
8	$ZrCl_4$ (10)	15
9	$SnCl_2{\cdot}2H_2O$ (10)	5
10	$FeCl_3$ (10)	5
11	PEG (1)	3
12	PEG (10)	8
13	PEG (20)	15
14	PEG (25)	25
15	PEG-OSO_3H (10)	98
16	PEG-OSO_3H (1)	38
17	PEG-OSO_3H (5)	78
18	PEG-OSO_3H (20)	99
19	PEG-OSO_3H (25)	99
20	None	15

Reaction conditions: 1,3-dicarbonyl compound (1 mmol), isatin (1 mmol), malononitrile (1 mmol), and H_2O (2 mL) stirred at 100 °C for 5 min

[a] Isolated yields of pure products

To optimize the reaction temperature, 1,3-cyclohexadione, isatin, and malononitrile in the presence of 5 or 10 mol% PEG-OSO_3H in water were reacted at different temperatures. Consequently, 10 mol% catalyst at 100 °C was selected as the best conditions for synthesis of oxindole. With decreasing temperature, the solubility of isatin and the catalyst decreased, therefore the rate of the reaction and the yield of the product decreased.

Table 3 Preparation of oxindole derivatives



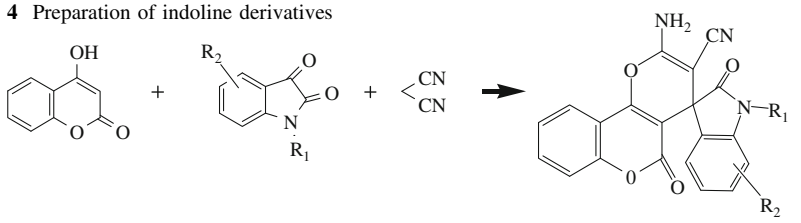
Entry	Reactant			Time (min)	Yield (%)[a]
	Dicarbonyl	Isatin			
	R_1	R_2	R_3		
1	H	H	H	5	98
2	H	H	5-NO_2	5	95
3	H	H	5-Br	7	89
4	H	H	5-Me	10	89
5	H	H	5-OMe	10	91
6	Me	H	H	5	90
7	Me	H	5-NO_2	5	93
8	Me	H	5-Br	5	91
9	Me	H	5-Me	10	93
10	Me	H	5-OMe	10	93
11	H	Et	5-NO_2	15	88
12	Me	Et	5-NO_2	10	88
13	H	$PhCH_2$	H	20	76
14	Me	$PhCH_2$	H	20	78
15	H	$PhCH_2$	5-Br	15	83
16	Me	$PhCH_2$	5-Br	15	86
17	H	H	4-Me	10	88
18	Me	H	4-Me	10	90
19	H	H	6-Me	10	85
20	Me	H	6-Me	10	88

Reaction conditions: dicarbonyl compound (1 mmol), isatin (1 mmol), malononitrile (1 mmol), catalyst (0.1 mmol), H_2O (2 mL) at 100 °C

[a] Isolated yields

To evaluate the catalytic activity of PEG-OSO_3H, the model reaction was performed in water (2 mL) at 100 °C for 5 min in the presence of different catalysts. The results are shown in Table 2, from which it is evident that PEG-OSO_3H was the most effective catalyst in terms of yield of oxindole (98 %); with other catalysts product yields were 3–45 % (Table 2, entries 1–14). To optimize the reaction conditions, we also changed the amount of catalyst. Consequently, the model condensation was best catalyzed by 0.1 mmol PEG-OSO_3H in water at 100 °C. Reaction with 5 mol% of catalyst required a longer reaction time and reaction with 1 mol% catalyst was incomplete even after 3 h and only 50 % of the

Table 4 Preparation of indoline derivatives



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

Reaction conditions: 4-hydroxycoumarin (1.0 mmol), isatin (1.0 mmol), malononitrile (1.0 mmol), catalyst (0.1 mmol), H_2O (2 mL) at 100 °C

[a] Isolated yields

product was obtained. Further increasing the amount of PEG-OSO_3H (20 mol%) had no significant effect on product yield (Table 2, entries 15–19). Control experiments indicated that in the absence of the catalyst, the reaction under the same conditions gave the oxindole in rather low yield (15 %) (Table 2, entry 20).

To further investigate the scope and limitations of this procedure under the optimized conditions (10 mol % catalyst in 2 mL H_2O at 100 °C), particularly with regard to library construction, this reaction was evaluated using a variety of isatin and 1,3-dicarbonyl compounds (Table 3). In all cases, the reaction proceeded readily, affording the corresponding oxindoles in high to excellent yields (76–98 %) in very short reaction times (5–20 min).

Reaction of dicarbonyl compounds with *N*-ethylisatin in the presence of 10 mol % PEG-OSO_3H proceeded well, giving the corresponding products in excellent yields without formation by products (Table 3, entries 11, 12). Reaction of dicarbonyls with *N*-benzylisatin required longer reaction times, however, and the products were obtained in lower yields (Table 3, entries 13–16). Dimedone reacted more quickly than 1,3-cyclohexadione analogues, possibly because of the presence of electron-donating groups (Me).

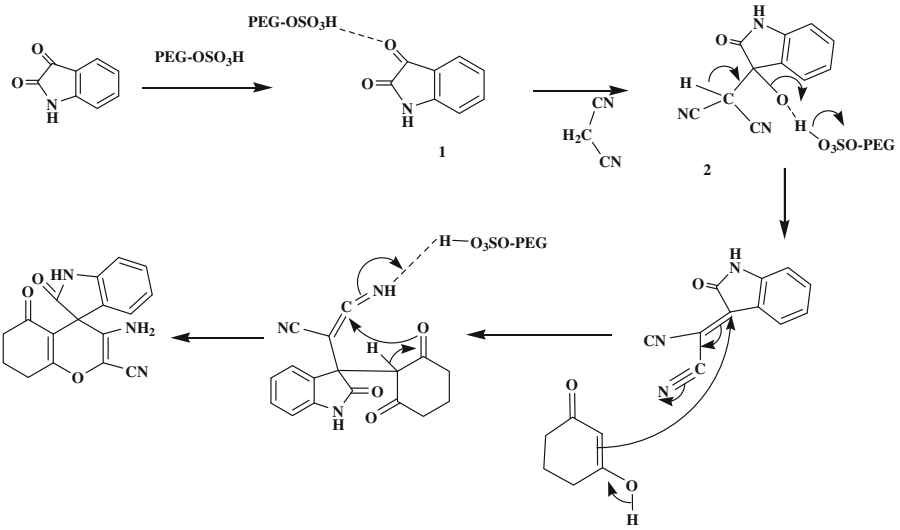
These reactions also proceeded with 4-hydroxycoumarin (Table 4), but reaction times were longer than for 1,3-diketones. This may be because 4-hydroxycoumarin

Table 5 Recyclability of PEG-OSO_3H as catalyst for synthesis of oxindoles

Entry	Cycle	Yield (%)[a]
1	0	98
2	1	95
3	2	92
4	3	88
5	4	87
6	5	85

Reaction conditions: 1,3-cyclohexadione (1 mmol), isatin (1 mmol), malononitrile (1 mmol), and H_2O (2 mL) stirred at 100 °C for 5 min

[a] Isolated yield of the pure product



Scheme 2 Mechanism proposed for synthesis of spiro oxindoles in the presence of PEG-OSO_3H

is less active than dicarbonyl compounds. In all cases, the product obtained was isolated by a simple filtration, washed with water, and purified by recrystallization from ethanol. The applicability of the method was also studied for phenolic compounds, for example phenol and resorcinol. We found that the reaction of phenols with isatin in the presence of this catalyst was not a straightforward reaction and after a prolonged reaction time (3 h) most of the starting materials remained intact.

It is worth mentioning that the catalyst is recyclable and could be reused without significant loss of activity. It could be recovered by filtration of the product, evaporation of the solvent, and washing with diethyl ether. The recycled catalyst could be used in another reaction. In the model reaction, yields from the first and subsequent experiments were almost identical for 5 runs (Table 5).

A reasonable pathway for the reaction of cyclohexadione, isatin, and malononitrile conducted in the presence of PEG-OSO_3H is presented in Scheme 2. The first step involves formation of activated isatin (**1**) followed by reaction of this with malononitrile to generate compound **2**. This subsequently undergoes elimination to produce compound of Knoevenagel condensation. Intermediate undergoes addition with cyclohexadione to afford the oxindole derivative. In this hypothesis, PEG-OSO_3H might serve as a Brønsted-acid catalyst in several stages.

Conclusions

In summary, an efficient procedure with PEG-OSO_3H as green acidic catalyst in water has been developed for preparation of spirocyclic(5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindole and tetrahydro[pyrano[3,2-*c*]quinoline]-4,3-indoline derivatives. The procedure has several advantages, including inexpensive and readily available catalyst, mild reaction conditions, high yields of the products, and simple experimental and isolation procedures. These make it a useful and an attractive procedure for synthesis of oxindole and indoline derivatives.

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