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Sulfonated polyethylene glycol as a reusable and efficient catalytic system for the synthesis of diindolyl oxindole derivatives under ambient conditions

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Abstract: Sulfonated Polyethylene Glycol (PEG-OSO_3H) as an efficient and reusable acidic catalyst was used for the preparation of 3,3-diheteroaromatic oxindole derivatives as an important class of potentially bioactive compounds from condensation reaction of indole and isatin derivatives under ambient conditions in good to excellent yields (65- 98%).

Keywords: Oxindole, PEG-OSO_3H, Indole, Isatin, Solid acid.

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. The use of polymer- supported catalysts has offered important advantages in organic synthesis such as operational simplicity, environmental compatibility, nontoxic, 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 glycol)s (PEGs) are highly favorable soluble polymeric matrixes and their molecular weight is >2000 dalton that have extensively been used as inexpensive and easily functionalized supports for the immobilization of catalysts. PEGs are readily soluble in water and polar organic solvents (e.g., dichloromethane, acetonitrile, DMF, DMSO) and insoluble in less polar solvents (e.g., hexane, diethyl ether, *tert*-butylmethyl ether). Therefore, exploiting this solubility property as a phase separation device, it is possible to use a PEG supported catalyst under homogeneous catalysis conditions (where the catalyst is expected to perform at its best) and, simply by decreasing the solvent polarity, to precipitate, recover, and recycle the catalyst. Because of this solubility profile, PEG-based supports combine high reactivity and analytical simplicity (advantageous features of homogeneous solution chemistry) and the 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 bronsted acid in promoting various organic transformation [3-9].

On a different note, oxindole derivatives often appear as important structural components in biologically active and natural compounds. Among oxindole systems, spirooxindoles have received considerable attention due to their wide range of useful biological properties, which include antibacterial, antiprotozoal, anti-inflammatory activities and progesterone receptors (PR) agonists [10-14]. For example, spirotryprostatins A and B, two natural alkaloids isolated from the fermentation broth of Aspergillus fumigatus, have been identified as novel inhibitors of microtubule assembly. Moreover, compound C "3'- amino-1'H-spiro[indole-3,4'-pyrazolo[4',3'.5,6]pyrano[3,2-d][1,3]oxazol]-2(1H)-one" has shown antimicrobial activity (Figure **1**) [15].

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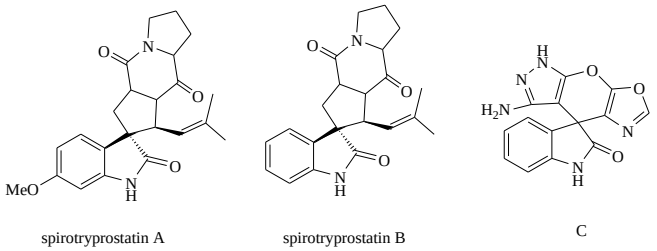


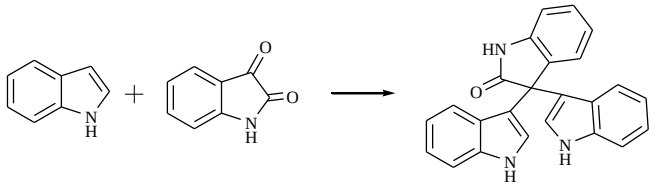
Figure 1: Biological active compounds based on spirooxindole derivatives.

In continuation of our work on the synthesis of biologically important compounds using simple, efficient, nontoxic, and readily available catalysts [16-18], we used PEG-OSO_3H for the synthesis of 3,3-diheteroaromatic oxindoles from the 2:1 coupling of indole and isatin derivatives under ambient condition in acetonitrile with good to high yields (65- 98%).

Results and discussion

PEG-OSO_3H was prepared via anchoring chlorosulfonic acid onto polyethylene glycol using a simple and convenient procedure [4]. This polymeric catalyst was used as an efficient bronsted acid 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 using various isatines and indoles. Indole and isatin were selected as the model substrates and reacted under different experimental variants (Scheme **1**). In preliminary experiment, this reaction was carried out in various solvents with PEG-OSO_3H (0.1 mmol) as a catalyst at room temperature (Table **1**). The results indicated that different solvents affected the efficiency of the reaction. THF, DMF, water, chloroform, DMSO and dichloromethane afforded low yields (Table **1**, entries 1-6). When ethylacetate, 1,2-dichloroethane, ethanol and methanol were used, the yields of the products increased (Table **1**, entries 7-10). Finally, when acetonitrile was used, the yield increased to 93% (Table **1**, entry 11) better than other solvents examined here. The reaction was carried out under solvent-free conditions and gave low yield (Table **1**, entry 12).



Scheme 1: Synthesis of 3,3-diindolyl oxindole.

To evaluate catalytic activity of PEG-OSO_3H, reactions of indole and isatin were carried out in acetonitrile (2 mL) at room temperature for 2.5 h in the presence of different catalytic systems, separately. As it is evident from the results (Table **2**), PEG-OSO_3H was the most effective catalyst in the term of yield of the oxindole (93%) while other catalysts formed the product with the yields of 5-20% (Table **2**, entries 1-9). To find optimized amount of PEG-OSO_3H, the reaction was carried out by varying amount of the catalyst (Table **2**, entries 10-14). In the presence of 1 mol% of catalyst, the model reaction was not completed even after 6 h and only 50% of the product was obtained. Further increases in the amount of PEG-OSO_3H (20 mol%) in mentioned reaction did not show any significant effect on the product yield. To establish the catalytic role of PEG-OSO_3H, indole was treated with isatin in the absence of catalyst. In this case, the reaction did not proceed over model reaction times (2.5 h) (Table **2**, Entry 15).

Among all the experimental variants, the reaction of PEG-OSO_3H (10 mol%) in CH_3CN at ambient temperature gave the best result with 93% yield.

To establish the generality and applicability of this method, indole and isatin compounds were subjected to the same reaction condition to furnish the corresponding oxindole derivatives. In all cases, the reactions gave the corresponding products in good to high yield (Table **3**). In the presence of this catalyst, isatin and isatin derivatives having an electron-withdrawing substituent were converted to their corresponding (bis-indolyl) oxindole in good to excellent yields (Table **3**, entries 1–12). It is delighted that isatin was reacted slower than those of electron-withdrawing substituents, which is probably due to more reactivity of carbonyl groups by electron-withdrawing groups. The reaction of indole compounds with N-methyl isatin proceeded well giving the corresponding product in excellent yields without formation of by-product, but the reaction of indole with N-benzyl isatin required higher molar ratios of the catalyst with longer reaction times and producing adducts in lower yields (Table **3**, entries 13-15). In all cases, the obtained product was isolated by a simple filtration, washed with CH_3CN or ethanol and purified by recrystallization from ethanol.

A reasonable pathway for the reaction of indole with isatin compounds conducted in the presence of PEG-OSO_3H is presented by Scheme **2**. The first step involves the formation of activated isatin (1) followed by its reaction with indole to generate compound 2 that subsequently undergoes elimination reaction to produce the compound 4. Intermediate 4 undergoes

further addition with the second indole molecule to afford oxindole derivatives.

Table 1: Effect of solvents on the reaction of indole and isatin catalyzed by PEG-OSO_3H[a].

So.nu	Solvent	Yield(%)[b]
1	THF	16
2	DMF	25
3	H_2O	10
4	$CHCl_3$	30
5	DMSO	30
6	CH_2Cl_2	45
7	EtOAc	50
8	$ClCH_2CH_2Cl$	55
9	EtOH	68
10	MeOH	65
11	CH_3CN	93
12	Solvent-free	10

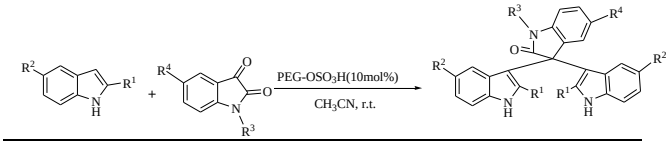
[a] The reactions were run under ambient condition for 2.5 h and the molar ratio of indole /isatin /catalyst was 2: 1: 0.1.
[b] Yields are related to isolated pure products.

Table 2: One-pot three-component synthesis of 3,3-diindolyl oxindole in the presence of various catalytic systems [a]

Entry	Catalyst(mol%)	yield(%)[b]
1	SiO_2 (10)	20
2	Al_2O_3 (acidic, 10)	18
3	Al_2O_3 (basic, 10)	20
4	Tetrabutylamonium chlorid(10)	5
5	Tetrabutylamonium hydrogen sulfat(10)	15
6	PEG (1)	5
7	PEG (10)	5
8	PEG (20)	10
9	PEG (25)	10
10	PEG-OSO_3H (1)	30
11	PEG-OSO_3H (5)	73
12	PEG-OSO_3H (10)	93
13	PEG-OSO_3H (20)	95
14	PEG-OSO_3H (25)	95
15	None	-

[a] Isatin (1 mmol), indole (1 mmol), CH_3CN (2 mL), stirred at room temperature for 2.5 h.
[b] Yields are related to isolated pure products.

Table 3: Synthesis of oxindoles catalyzed by PEG-OSO_3H[a]



Entry	Reactant: Indole R^1	Indole R^2	Isatin R^3	Isatin R^4	Time(h)	Yield(%)
1	H	H	H	H	2.5	93
2	Me	H	H	H	2	92
3	H	Br	H	H	5	78
4	H	H	H	Cl	2	93
5	Me	H	H	Cl	1.5	92
6	H	Br	H	Cl	5	85
7	H	H	H	Br	2.5	85
8	Me	H	H	Br	1.5	95
9	H	Br	H	Br	5	78
10	H	H	H	NO_2	3.5	93
11	Me	H	H	NO_2	3	98
12	H	Br	H	NO_2	5	93
13	H	H	$PhCH_2$	H	2.5	72
14	Me	H	$PhCH_2$	H	2.5	82
15	H	Br	$PhCH_2$	H	2.5	65
16	H	H	Me	H	2.5	86
17	Me	H	Me	H	2.5	89
18	H	Br	Me	H	2.5	74

[a]Reaction conditions: isatin compounds (1 mmol), indole compounds (2 mmol), PEG-OSO_3H (0.1 mmol H^+) and CH_3CN (2 mL) at room temperature.
[b] The yield refers to pure isolated product.

It is noteworthy to mention that the catalyst is recyclable and could be reused without significant loss of activity. It could be recovered by filtration of product, evaporation of solvent and washing with diethyl ether. The recycled catalyst was reused in the model reaction. The results of the first experiment and the subsequent were almost consistent in yield after five runs (Table **4**).

Table 4: Recyclability of PEG-OSO_3H as a catalyst in synthesis of oxindoles [a]

Entry	Cycle	Yield (%)[b]
1	0	93
2	1	91
3	2	91
4	3	90
5	4	88

[a]Reaction conditions: isatin (1 mmol), indole (2 mmol), PEG-OSO_3H (0.1 mmol H^+) and CH_3CN (2 mL); reactions conducted for 2.5 h at room temperature.
[b] The yield refers to pure isolated product.

Conclusion

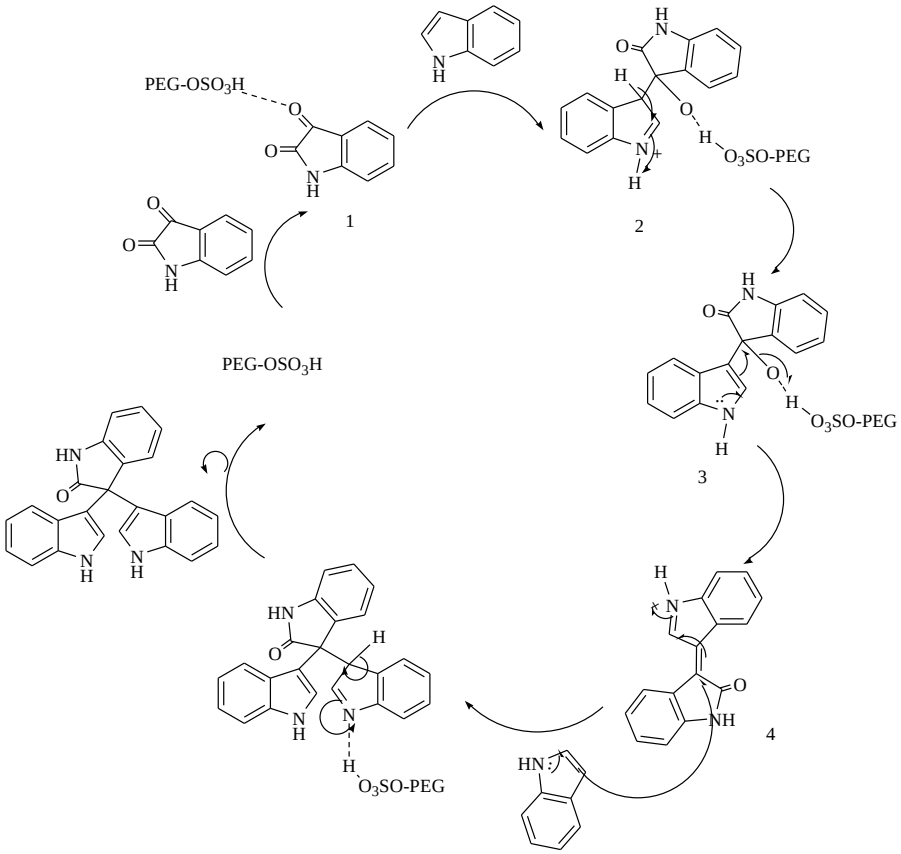
In summary, an efficient protocol for the preparation of 3,3-diheteroaromatic oxindole derivatives in acetonitrile using PEG-OSO_3H as inexpensive catalyst was described. The reactions were carried out under ambient conditions with short reaction time and produce the corresponding products in good to excellent yields. The catalyst is reusable, safe, and inexpensive without need for the application of chromatographic methods in the work-up procedure.

Experimental

Materials and apparatus:

Isatin and indole compounds were purchased from Merck Chemical Company. Purity determinations of the products were 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}. ^1H 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.



Scheme 2: The proposed mechanism for the synthesis of 3, 3- diindolyl oxindole in the presence of PEG-OSO_3H.

Preparation of PEG-OSO_3H:

PEG-OSO_3H was synthesized according to the literature procedure [4]. At 0 ^0C, 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). Then, the resulting solution was stirred at room temperature overnight, and the solution was concentrated under vacuum. Diethyl ether (10 mL) was added to the concentrated solution, the precipitate filtered and washed with ether (30 mL) three times to afford the PEG-OSO_3H. The number of H^+ sites on the PEG-OSO_3H was determined by acid-base titration.

Procedure for the synthesis of oxindoles:

A mixture of the indole (2 mmol), isatin (1 mmol) and PEG-OSO_3H (10 mol%) in acetonitril (2 mL) was stirred at room temperature for the appropriate time (Table **3**). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with acetonitril. The crude solid product was crystallized from EtOH to afford the pure oxindole.

Spectral data for selected products:

3,3-Diindolyloxindole (compound 1). White Solid, m.p> 250^oC; ^1H NMR (250 MHz, DMSO-d_6) 6.79 (2H, m, ArH), 6.84 (2H, m, ArH), 6.92 (1H, m, ArH), 6.97–7.02 (3H, m, ArH), 7.22 (4H, m, ArH), 7.35 (2H, m, ArH), 10.58 (1H, s, N–H), 10.94 (2H, br s, N–H); ^{13}C NMR (62.9 MHz, DMSO) 53.4, 110.4, 112.4, 115.2, 119.1, 121.6, 121.8, 122.3, 125.1, 125.8, 126.6, 128.7, 135.5, 137.8, 142.2, 179.6; IR (KBr, cm^{-1}) 3420, 3300, 1704, 1610, 1105, 737 cm^{-1}; Anal. Calcd for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.56. Found: C, 79.39; H, 4.68; N, 11.63.

3,3-Bis(2-methylindolyl)oxindole (compound 2). White Solid, m.p> 250 ^oC; ^1H NMR (DMSO-d_6) 1.95 (3H, s, Me), 2.09 (3H, s, Me), 6.47 (1H, m, ArH), 6.61–6.66 (2H, m, ArH), 6.71 (1H, m, ArH), 6.85–6.92 (3H, m, ArH), 6.96 (1H, m, ArH), 7.16 (1H, m, ArH),

7.21–7.24 (3H, m, ArH), 10.57 (1H, s, NH), 10.87 (1H, s, NH), 10.90 (1H, s, NH) ppm; ^{13}C NMR (DMSO-d_6) 13.87, 14.05, 53.28, 110.21, 110.29, 111.21, 111.27, 118.78, 118.84, 120.15, 120.21, 120.46, 120.63, 122.13, 126.32, 127.90, 128.54, 128.68, 132.84, 134.81, 135.76, 135.83, 136.44, 142.06, 180.21 ppm; IR (KBr, cm^{-1}) 3400, 3250, 1700 cm^{-1}; Anal. Calcd for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.85; H, 5.32; N, 10.64.

3,3-Diindolyl-5-bromooxindole (compound 3). White Solid, mp> 250 ^oC; ^{1}H NMR (DMSO-d_6) 6.81 (2H, t, ArH), 6.88 (2H, s, ArH), 6.96 (1H, m, ArH), 7.03 (2H, m, ArH), 7.21 (2H, m, ArH), 7.30 (1H, s, ArH), 7.38 (2H, m, ArH), 7.43 (1H, m, ArH), 10.77 (1H, s, NH), 11.03 (2H, s, NH) ppm; ^{13}C NMR (DMSO-d6) 53.64, 112.65, 114.00, 114.35, 119.23, 119.35, 121.35, 121.94, 125.21, 125.35, 126.34, 128.22, 137.79, 137.84, 141.53, 179.11 ppm; IR (KBr, cm^{-1}): 3340, 3120, 1699 cm^{-1}; Anal. Calcd for C_{24} $H_{16}BrN_3O$: C, 65.17; H, 3.65; N, 9.50. Found: C, 65.11; H, 3.49; N, 9.62.

Acknowledgments

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