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Facile synthesis of ninhydrin and isatin based hydrazones in water using PEG-OSO_3H as a highly efficient and homogeneous polymeric acid-surfactant combined catalyst

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Abstract: The synthesis of a series of biologically important ninhydrin and isatin based hydrazones has been carried out by refluxing easily synthesized novel *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates with ninhydrin and isatins in presence of PEG-OSO_3H as catalyst in water medium. The dual characteristic of PEG-OSO_3H as a Brønsted acid as well as a phase-transfer catalyst is successfully exploited in these synthesis. Reduced reaction time, operational simplicity, excellent yields of the products with high purity, and more importantly, easy recoverability and reusability of the homogeneous polymeric catalyst make the reaction an attractive, economic and sustainable green synthetic methodology.

Keywords: Hydrazone derivatives, Ninhydrin, Isatin, *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates, PEG-OSO_3H, Water medium.

Hydrazones possess various important bioactivities such as antimicrobial,[1] anticonvulsant,[2] analgesic,[3] anti-inflammatory,[4] antiplatelet,[5] and antitumoral[6] activities. The hydrazone derivatives of isatin are also used as plasticizers and antioxidants,[7] β-secretase-1 (BACE 1) inhibitors,[8] commercial herbicides and acetohydroxyacid synthase inhibitor.[9] Not only that, ninhydrin and isatin based hydrazones also have large applications to act as

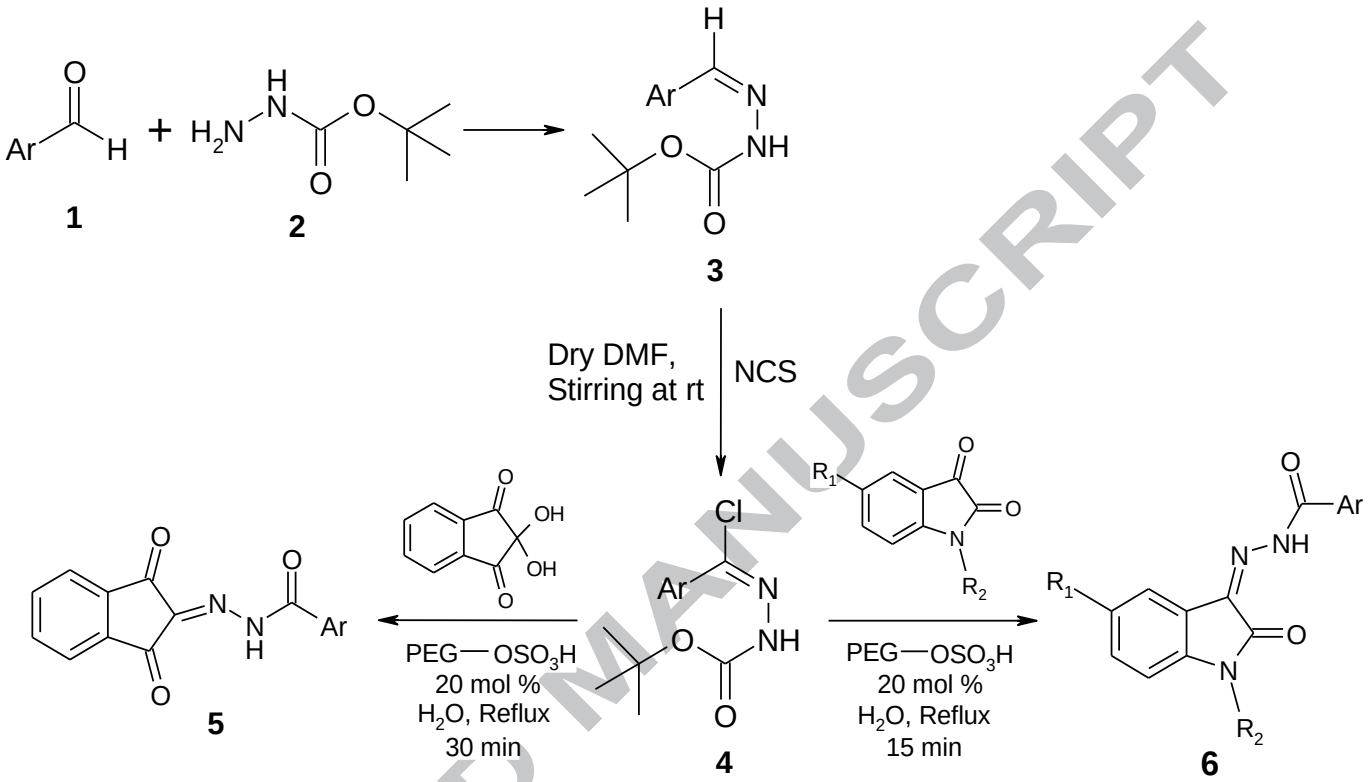
potential ligands in several metal bound complex formation.[10,11a,b] In the literature, only one hydrazone derivative of ninhydrin[10] and that of many isatin derivatives are reported.[8,9,11] Generally, these biologically active hydrazone derivatives are synthesized by refluxing or stirring several arylhydrazides with isatins or ninhydrin in various mediums like AcOH, methanol, ethanol, ethanol-AcOH mixed solvent *etc.*[8,11a-h] or in solid state.[11i] Commercially, limited numbers of arylhydrazides that are available are quite costly.[12] In laboratory, arylhydrazides are generally prepared, converting the aromatic acids into acid chloride by the treatment with hazardous thionyl chloride, followed by the reflux with hydrated hydrazine hydride,[13] or by refluxing the mixture of aromatic esters with excess hydrazine hydride.[9,14] In both cases, refluxing with hydrazine hydride requires a long period of time, which is followed then by 24 h cooling.[9,13,14] In this context, an eco-friendly green synthetic methodology within short reaction period should be devised to synthesize these biologically important hydrazone derivatives.

Nowadays, green chemistry has attained the status of a major scientific discipline.[15] The development of simple and efficient chemical processes or methodologies within the frame of green chemistry[16] for the synthesis of biologically important compounds in water medium is in demand. Although water is a safe, very cheap, most abundant, and environmentally benevolent solvent, organic synthesis in water medium is quite challenging for several reasons: sluggish reaction rate due to solubility problems, deactivation of reagents in water etc.[17] These problems can be minimized or overcome by developing a synthetic methodology in presence of surfactant combined catalyst. In this context, chlorosulphonic acid-modified PEG-6000 (PEG-OSO_3H)[18] is an interesting example of mild, non-volatile and non-corrosive Brønsted acid-phase transfer homogeneous polymeric catalyst[19b,c] with an intriguing solubility profile e.g. it is soluble in many polar solvents including water and methanol and insoluble in non-polar solvents such as hexanes, diethyl ether *etc.* The use of

this catalyst is highly expedient in organic synthesis because of simplified working procedures, easy separation of products without discharging any harmful waste and reusability of catalyst.[19] As an acid catalyst, it can activate the substrate molecules and as a surfactant, it increases the concentration of organic reactants to form micelle particles in water.[20] Considering the highly advantageous uses of PEG-OSO_3H as acid-surfactant combined catalyst, and in continuation of our research work with novel *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates,[21] herein, we wish to report a new, economic, mild, rapid, and highly efficient green procedure to synthesize biologically important hydrazones of ninhydrin and isatins from *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates in presence of inexpensive, reusable, bio-degradable and environmentally benign PEG-OSO_3H in water medium (Scheme 1).

In our present work, we have synthesized several hydrazone derivatives of ninhydrin **5** and isatins **6** (Scheme 1), in which ninhydrin and several isatin derivatives were condensed with differently substituted arylhydrazides, generated *in situ* from *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates **4** through acid catalyzed reaction. Initially a series of carbo-*tert*-butoxyhydrazones **3** were prepared by the condensation of aromatic aldehydes **1** with *tert*-butylcarbazate **2**. Subsequently, the compounds **3** were treated with *N*-chlorosuccinamide in dry DMF medium to get *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates **4** in very high yields.[21,22] Then a mixture of ninhydrin and *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates **4** was refluxed in presence of PEG-OSO_3H (20 mol %) in water medium for 30 min. The yellow solid products **5** were precipitated out from the reaction mixture while cooling. In a similar way, isatin and *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates **4** were refluxed in presence of PEG-OSO_3H (20 mol %) in water medium for 15 min to get the reddish yellow products **6** on cooling the reaction mixture.[22] In all cases, the final products were confirmed

by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, X-ray diffraction study (Fig. 1)[23] and also by comparing the melting points of **6** with the reported values.



Scheme 1. Formation of *N′*-(1,3-dioxo-indan-2-ylidene)-arylhydrazides **5** and *N′*-(2-oxo-1,2-dihydro-indol-3-ylidene)-arylhydrazides **6**.

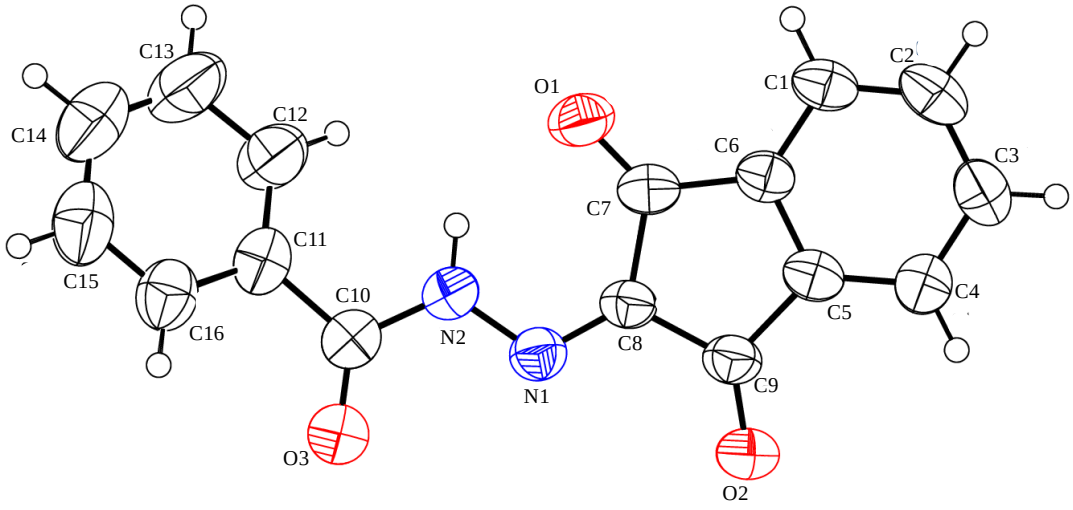
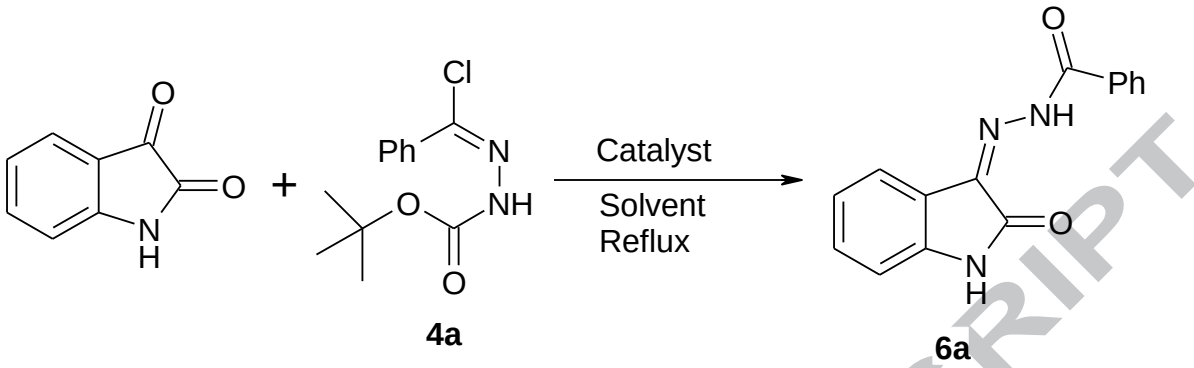


Figure 1. ORTEP diagram of compound **5a** (Ar=Ph) with atom numbering scheme. Thermal ellipsoids are shown at the 50% probability. (CCDC No. 919629)



Scheme 2. Synthesis of *N′*-(2-oxo-1,2-dihydro-indol-3-ylidene)-benzohydrazide **6a** using isatin and *N′*-(chloro-phenyl-methylene)-*tert*-butylcarbazate **4a**

At first, we chose the model reaction between isatin and *N′*-(chloro-phenyl-methylene)-*tert*-butylcarbazate (**4a**) in 1.20: 1.00 molar ratio under refluxing condition in water medium (Scheme 2, Table 1, entry 1). But yield of the product was very low (<5%). In the absence of any catalyst, on varying the reaction medium from ethanol, acetonitrile to acetic acid, the yield of the reaction increases intriguingly from 5% to 68% (Table 1, entry 2-4). From this result, we envisioned that a Brønsted acid activation was essential for initiation and higher yield of this reaction to achieve. The structure of the product **6a** was assigned and confirmed by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, elemental analysis and also by matching the melting point of the product with the reported value.[11e] These significant results motivated us to test the reaction at higher acidic condition. We increased the acidic strength of the acetic acid solution of the reaction mixture by adding a few drops of H_2SO_4. But the reaction mixture gets charred instantaneously with no product formation. It suggested that harsh reaction condition was not suitable for performing the reaction (Table 1, entry 5). To obtain the desired product with satisfactory yield under milder reaction condition, we tested several Brønsted catalysts such as HCl, *p*-TSA, and acetic acid etc. along with some organo-acid catalysts *e.g.* lactic acid, formic acid and citric acid in water medium (Table 1, entry 6-11).In all these cases, the desired product was isolated with considerable purity, but

unsatisfying yield. Interestingly we observed that the yield of the reaction improved significantly (78%) when melamine sulfonic acid (MSA) was employed as the insoluble solid acid-catalyst (Table 1, entry 12). This observation motivated us to choose a Brønsted acid-phase transfer catalyst (PTC) which could help the reaction to run in water medium smoothly with easier work-up procedure and operational simplicity. At first, we performed the model reaction taking PEG_{400}-OSO_3H as the acid-surfactant combined catalyst. Though the reaction time was reduced to 45 min, yield of the product was moderate (48%), (Table 1, entry 13). On increasing the molecular weight of polyethyleneglycol hemisulfates and hence the size of the crown-shape moiety (PEG_{4000}-OSO_3H), reaction time was further diminished to 25 min and yield of the product became moderate to good (69%), (Table 1, entry 14). Gratifyingly, PEG_{6000}-OSO_3H gave our desired product in almost quantitative yield and with concomitant reduction of reaction time (from 60 min to 15 min) (Table 1, entry 17). On varying the percentage of catalyst load (10 mol% - 25 mol %), maximum yield of the product (95%) was obtained at 20 mol % (Table 1, entry 16-19). Similar optimization study was also carried out with ninhydrin (1.00 mmol) and *N'*-(chloro-phenyl-methylene)-*tert*-butylcarbazate (**4a**) (1.00 mmol) in presence or absence of various catalysts under refluxing condition in different solvents. Best yield of the desired product within a short span of reaction time was achieved with PEG-OSO_3H (20 mol%) in water medium (86%) (See supplementary material). On the basis of these promising results with PEG-OSO_3H as catalyst and water as the reaction medium, we had performed a library synthesis of several hydrazone derivatives of ninhydrin and isatins (Table 2 and Table 3).

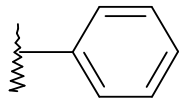
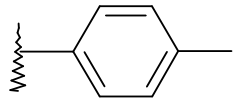
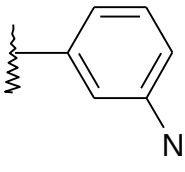
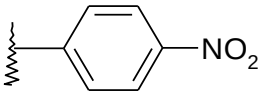
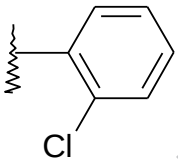
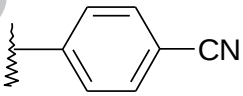
Table 1. Optimization of reaction conditions for the synthesis of **6a** from **4a**

Entry	Solvent	Catalyst	Catalyst Load (mol %)	Time (min)	Yield (%)[a]
1	H_2O	—	—	60	<5
2	Acetonitrile	—	—	60	5
3	Ethanol	—	—	60	12
4	Acetic acid	—	—	60	68
5	Acetic acid	H_2SO_4	20	—	—
6	H_2O	HCl	20	15	61[b]
7	H_2O	*p*-TSA	20	60	27
8	H_2O	Acetic acid	20	60	44
9	H_2O	Lactic acid	20	60	42
10	H_2O	Formic acid	20	60	25
11	H_2O	Citric acid	20	60	37
12	H_2O	Melamine sulfonic acid (MSA)	20	60	78
13	H_2O	HO_3SO-PEG_{400}-OSO_3H	20	45	48
14	H_2O	HO_3SO-PEG_{4000}-SO_3H	20	25	69
15	H_2O	HO_3SO-PEG_{6000}-OSO_3H	10	15	81
16	H_2O	HO_3SO-PEG_{6000}-OSO_3H	15	15	86
17	**H_2O**	**HO_3SO-PEG_{6000}-OSO_3H**	**20**	**15**	**95**
18	H_2O	HO_3SO-PEG_{6000}-OSO_3H	25	15	95

[a] Isolated yield.

[b] After 15 min, the reaction mixture started to get charred.

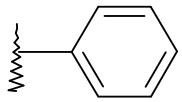
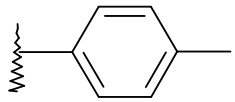
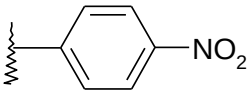
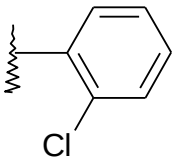
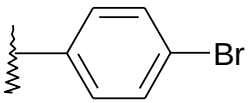
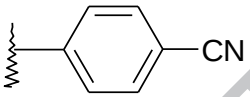
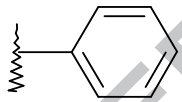
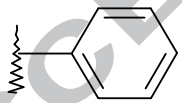
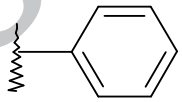
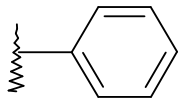
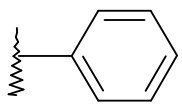
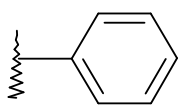
Table 2. Formation of hydrazones **5** from **4**

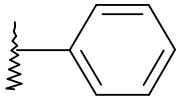
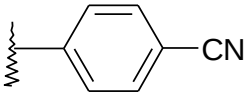
Entry	Ar	Adduct	Product	Yield (%)[a,b]	Melting point(ºC)
1		**4a**	**5a**	86	200-201
2		**4b**	**5b**	83	163-164
3		**4c**	**5c**	81	258-260
4		**4d**	**5d**	88	234-236
5		**4e**	**5e**	80	190-191
6		**4f**	**5f**	85	208-209
7		**4g**	**5g**	87	174-176
8		**4h**	**5h**	85	202-204
9		**4i**	**5i**	89	238-240

[a]Isolated yield

[b]All the reactions were performed for 30 min.

Table 3. Formation of hydrazones **6** from **4**

Entry	Ar	Adduct	R_1	R_2	Product	Yield (%)[a,b]	Lit m.p[11]/ Observed m.p (ºC)
1		**4a**	H	H	**6a**	95	278[11e]/ 284-286
2		**4b**	H	H	**6b**	93	284-286[c]
3		**4d**	H	H	**6c**	90	>265[11e]/ >300
4		**4e**	H	H	**6d**	88	>270[11f]/ 282-284
5		**4f**	H	H	**6e**	87	235[11g]/ 234-236
6		**4h**	H	H	**6f**	89	>300[c]
7		**4i**	H	H	**6g**	96	>300[c]
8		**4a**	F	H	**6h**	94	>300[c]
9		**4a**	Cl	H	**6i**	95	>275[11h]/ >300
10		**4a**	Br	H	**6j**	91	>260[11h]/ >300
11		**4a**	I	H	**6k**	89	290-292[c]
12		**4a**	NO_2	H	**6l**	92	>300[c]
13		**4a**	H	Me	**6m**	86	179-180[11h]/180-182

14		**4a**	H	Et	**6n**	84	164-165[c]
15		**4i**	H	Et	**6o**	88	194-196[d]

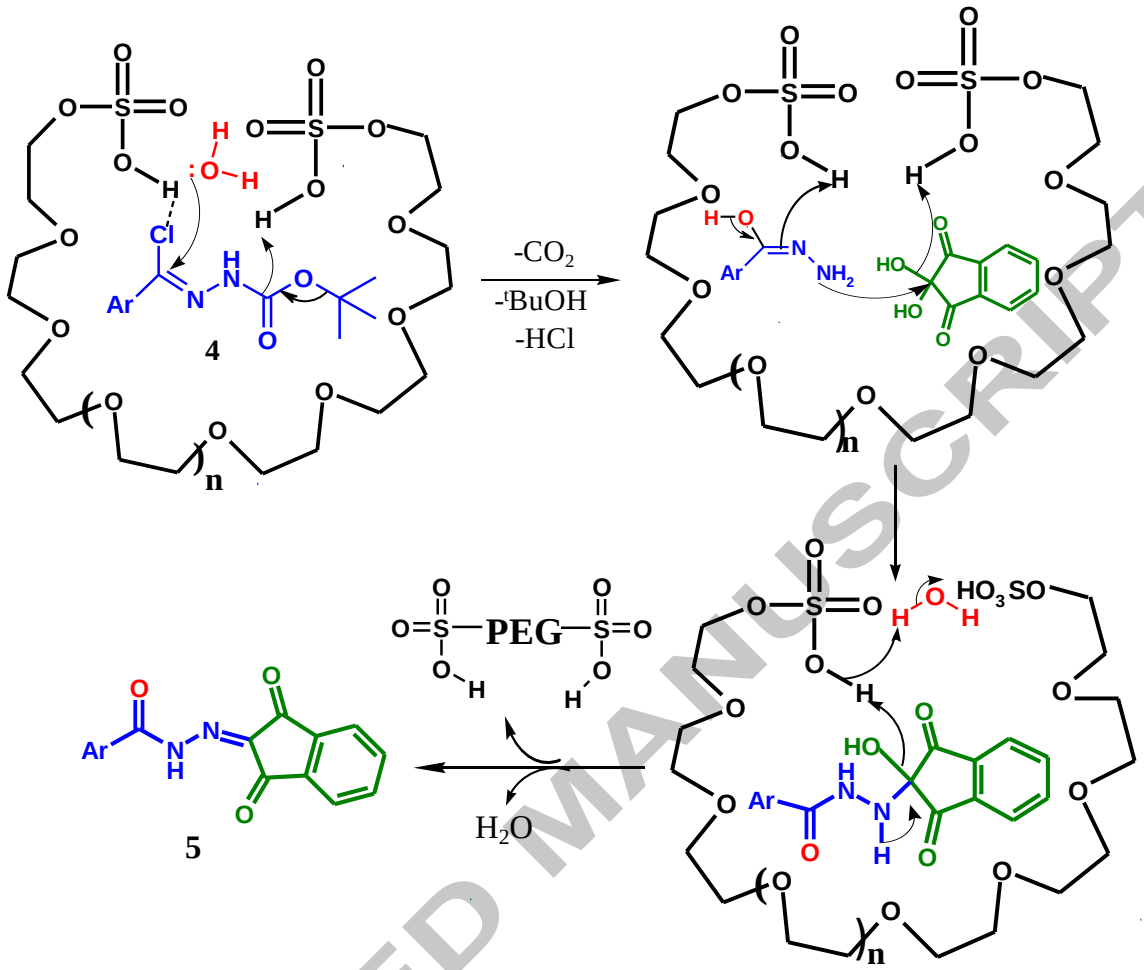
[a]Isolated yield.

[b]All the reactions were performed for15 min.

[c]In the literature, melting points of these compounds are not reported, formation of these compounds were confirmed on the basis of spectral analyses..

[d]The compound is new.

A reasonable mechanistic aspect has been depicted for the formation of hydrazone derivatives of ninhydrin and isatin from *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates **4** in Scheme 3. At first, the carbon centre, having C-Cl bond of compound **4** becomes electronically deficient due to the activation by the -SO_3H group of PEG-OSO_3H catalyst which instigates the solvent water molecule to attack. Simultaneously the acid catalyzed removal of Boc group leads to *in situ* formation of arylhydrazides which subsequently condenses with the C-2 carbon of ninhydrin and C-3 position of isatins, assisted by the Brønsted acidity of PEG-OSO_3H catalyst to furnish the final product **5** and **6** respectively. Excellent yield of the product may be attributed to the fact that, the hydrophobic supramolecular cavity of the catalyst encapsulates the organic substrates, brings them closer to one another and after the formation of the product via several intermediates through the activation of reactants, the product gets precipitated out from the reaction mixture due to its insolubility in water. Rapid exclusion of water molecules from the hydrophobic core of the catalyst, generated during the condensation reactions may also facilitate the condensations.



Scheme 3. Plausible reaction pathway for the formation of compounds **5**

Furthermore, a recovering and reusability test of PEG-OSO_3H for the formation of **6a** was performed up to five times without any serious loss of its activity or efficiency. After refluxing the mixture of isatin, *N*′-(chloro-phenyl-methylene)-*tert*-butylcarbazates **4a** and PEG-OSO_3H in water medium for 15 min, the product (insoluble in water) was simply filtered and washed with methanol for purification. In order to recover the catalyst, methanol and water were evaporated under reduced pressure, and the resulting gummy mass was washed with diethylether, and dried. The recovered catalyst was reused directly for a new reaction cycle and after five consecutive cycles, the yield of the product **6a** varied from 95-88% (Figure 2).

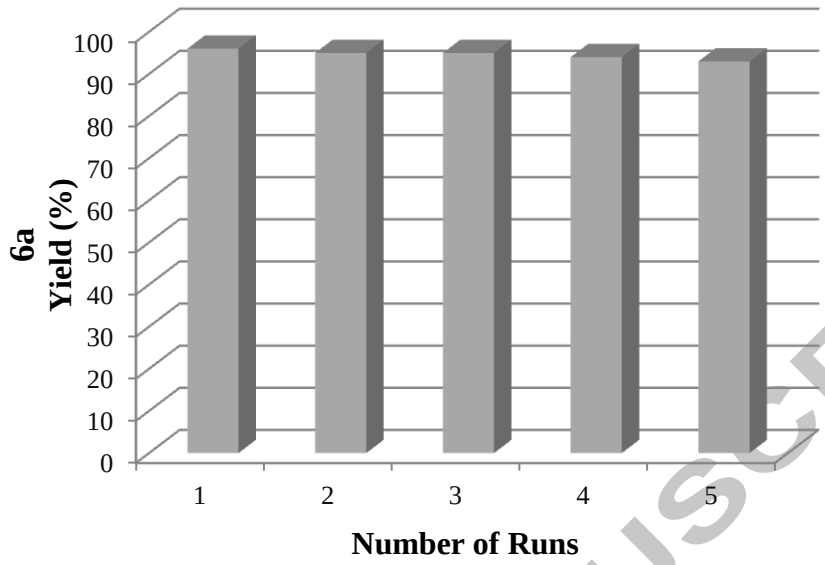


Figure 2. Reuse of PEG-OSO_3H in the synthesis of **6a**

In conclusion, we have successfully developed a highly efficient, general and green synthetic methodology for the hydrazone derivatives of ninhydrin and isatin, using PEG-OSO_3H as a recoverable and biodegradable polymeric catalyst in water medium. Cost effectivity, mild reaction conditions, operational simplicity, enhanced rates, ease of handling of the catalyst, cleaner reaction profile, high isolated yields of pure products and use of water as the solvent are the significant advantages of the procedure described here.Therefore this may be a very attractive method for the synthesis of this biologically active hydrazone library in chemical and pharmaceutical industries fulfilling the demand of the green chemistry protocols.

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Single Crystal Diffractometer Facility at the Department of Chemistry, University of Calcutta.

Supporting Information

Supplementary data (IR, ^{1}H, ^{13}C data of compounds **5** and **6** and crystallographic data for **5g**) associated with this article can be found, in the online version, at ----------

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18. **Preparation of PEG-OSO_3H:** At 0 ^oC, chlorosulfonic acid (10 mmol) was added to a solution of PEG-6000 (1 mmol) in CH_2Cl_2 (10 mL), and the resulting solution was stirred at room temperature overnight. Then, the solution was concentrated under vacuum, and ether was added to it. The resulting precipitate was filtered and washed with ether three times to afford PEG-OSO_3H as a gummy solid.[19a] ^{1}HNMR ($CDCl_3$, 500 MHz): (ppm) δ3.40–3.54 (m, PEG), 4.18 (s, 2H, CH_2OSO_3H), 12.69 (s, 1H, SO_3H).

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22. **General procedure for the synthesis of *N′*-(chloro-aryl-methylene)-*tert*-butylcarbazates (4):** Aromatic aldehydes **1** (1.00 mmol) and *tert*-butylcarbazate **2** (1.00 mmol) were placed in a 50 ml round bottomed flask where condensation between **1** and **2** took place instantaneously to form the carbo-*tert*-butoxyhydrazones **3**. In the case of solid aldehydes, 5.0 ml of methanol was required to add to the mixture of **1** and **2** and heated slightly on water bath to furnish the condensation. Subsequently, *N*-chlorosuccinamide (1.00 mmol) was added to the dry DMF (10 mL) solution of compounds **3** (1.00 mmol) at cold condition (temperature around 0 ^oC) and then stirred for 3 h at room temperature. The

progress of the reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was poured into ice-cold water and the solid residue **4** was filtered out, which was washed several times with distilled water, dried in open air and then crystallized from acetone.

Typical procedure employed for the synthesis of *N′*-(1,3-dioxo-indan-2-ylidene)-benzohydrazide (5a): A mixture of ninhydrin (0.178 g, 1.00 mmol), *N′*-(chloro-phenyl-methylene)-*tert*-butylcarbazates (**4a**) (0.254 g, 1.00 mmol), and PEG-OSO_3H (20 mol %) was refluxed in water (10 mL) for 30 min. Progress of the reaction was monitored by TLC checking. A yellow solid product was precipitated out from the reaction mixture while cooling. The crude yellow solid product **5a** was isolated through filtration and washed thoroughly with water for several times. Then the compound **5a** was crystallized from methanol.

Typical procedure employed for the synthesis of *N′*−(2-oxo-1,2-dihydro-indol-3-ylidene)-benzohydrazide (6a): A mixture of isatin (0.176 g, 1.20 mmol), *N′*-(chloro-phenyl-methylene)-*tert*-butylcarbazates (**4a**) (0.254 g, 1.00 mmol), and PEG-OSO_3H (20 mol %) was refluxed in water (10 mL) for 15 min. Progress of the reaction was monitored by TLC checking. A reddish-yellow solid product was precipitated out from the reaction mixture while cooling. The crude yellow solid product **6a** was isolated through filtration and washed thoroughly with water-methanol to afford pure product **6a**.

Representative spectral data of compounds: *N′*-(1,3-dioxo-indan-2-ylidene)-benzohydrazide (5a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.79 (bs,1H), 8.10-7.89 (m, 6H), 7.69-7.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 184.4, 162.3, 141.9, 139.3, 138.1, 137.1, 136.9, 136.3, 133.5, 131.0, 129.0, 128.5, 124.0; IR (KBr): 3076, 1725, 1692 cm^{-1}; Anal calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07% Found C, 68.97; H, 3.55; N, 10.00%.

***N′*-(1,3-dioxo-indan-2-ylidene)-4-nitro-benzohydrazide (5d):** ^{1}H NMR (300 MHz, d_6-DMSO): δ 13.43 (s,1H), 8.38 (d, *J*= 8.7 Hz, ,2H), 8.08 (d, *J*= 8.7 Hz, 2H), 7.96 (m, 4H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 186.9, 185.2, 164.2, 150.3, 141.8, 141.0, 139.8, 137.3, 137.2, 137.0, 130.0, 124.5, 124.2, 123.8; IR (KBr): 3079, 1727, 1690 cm^{-1}; Anal calcd for $C_{16}H_9N_3O_5$: C, 59.45; H, 2.81; N, 13.00% Found C, 59.36; H, 2.73; N, 12.94%.

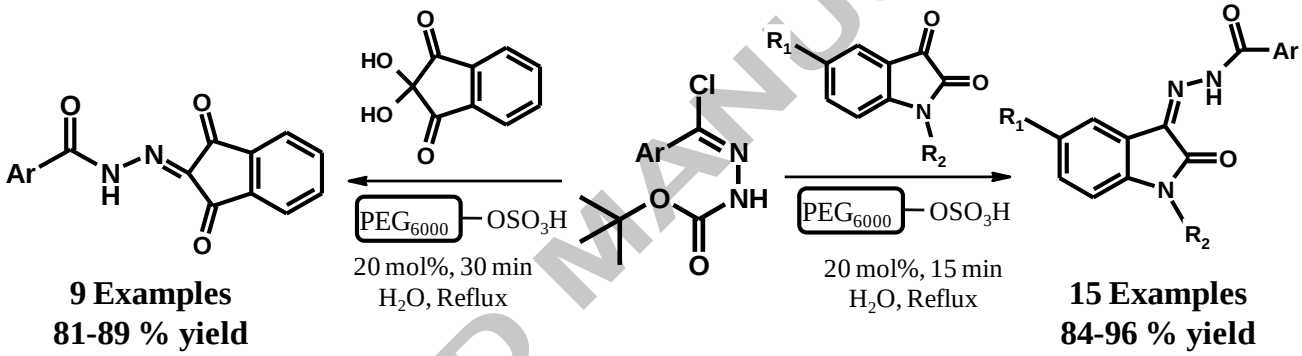
***N′−(1-ethyl-2-oxo-1,2-dihydro-indol-3-ylidene)-4-cyano-benzohydrazide* (6o):** ^{1}H NMR (300 MHz, d_6-DMSO): δ; 13.88 (bs, 1H), 8.08-7.89 (m, 4H), 7.61-7.43 (m, 2H), 7.22-7.12 (m, 2H), 3.78 (q, *J*= 6.9 Hz, 2H), 1.20 (t, *J*= 6.6 Hz, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 161.2, 143.2, 136.4, 133.5, 132.5, 129.5, 128.7, 127.9, 123.7, 121.4, 119.5, 118.5, 115.4, 110.6, 34.8, 12.9; IR (KBr): 2227, 1696, 1679 cm^{-1}; Anal calcd for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60% Found C, 67.83; H, 4.36; N, 17.52%.

23. Crystallographic data for the structure **5a** and **5g** in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 919629, and 919941 respectively. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Graphical abstract

Facile synthesis of ninhydrin and isatin based hydrazones in water using PEG-OSO_3H as a highly efficient and homogeneous polymeric acid-surfactant combined catalyst

Kamalesh Debnath, Sudipta Pathak and Animesh Pramanik*



9 Examples
81-89 % yield

15 Examples
84-96 % yield