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Synthesis of Schiff and Mannich bases of isatin derivatives and isatin hydrazones using ultrasonic irradiation in the presence of PEG–SO_3H

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ABSTARCT

Ultrasonic-assisted as a green approach used for the synthesis of Schiff and Mannich bases of isatin derivatives and isatin hydrazones. It can be proceed by using condensation reaction of amines, hyrazines, thiosemicarbazide and semicarbazide with isatin derivatives, in the presence of catalytic amounts of PEG–SO_3H, in EtOH, at 80 ˚C. High conversions, short reaction times and a cleaner reaction profiles are some of the advantages of this method.

Keywords: Ultrasound irradiation, Schiff and Mannich bases of isatin derivatives and isatin hydrazones, PEG–SO_3H.

INTRODUCTION

Ultrasound irradiation has been increasingly used in organic synthesis and synthesis of biologically significant molecules in the last three decades as an eco-friendly energy source. Compared to traditional methods, this technique is more convenient and easily controlled [1-3]. Moreover, enhanced reaction rates, formation of cleaner products and waste minimization are some prominent features of this technology [4, 5]. More recently, ultrasonic irradiation has been used for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones [6], 1,3-dipolar cyclo addition [7] and multi component reaction [8] as a clean, practical and of use protocol.

Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds *via* ring closure, cycloaddition and replacement reactions [9]. Schiff and Mannich bases of isatin derivatives are reported to demonstrate variety of biological activities like antibacterial [10], antifungal [11], anticonvulsant [12], anti HIV [13], antidepressant [14], and anti inflammatory [15] activities. In addition, is at in hydrazones have been reported to possess anticonvulsant activity [16].

Sulfonated polyethylene glycol (PEG–SO_3H) as a inexpensive, acidic, non-corrosive, eco-friendly and versatile catalyst has been used for the synthesis of several heterocyclic molecules such as synthesis of bis(indolyl-pyrazolyl)methanes [17], 14-aryl-14H-dibenzo[a,j]xanthenes [18] and coumarin and uracil fused pyrrole derivatives [19].

Furthermore PEG–SO_3H catalyses several organic reactions including ring opening of epoxides [20], Beckmann rearrangement and dehydration of oximes [21]. In addition, PEG–SO_3H is a homogeneous catalyst, soluble in a number of solvents including water, thus eliminating the problems associated with heterogeneous catalysts such as poorer reactivity, extended reaction times and sometimes, toxicity.

Hence, we make our minds up to synthesize Schiff and Mannich bases of is at in derivatives and is at in hydrazones, by using ultrasound irradiation at EtOH and in the presence of catalytic amounts of PEG–SO_3H.

MATERIALS AND METHODS

General. All chemicals were obtained commercially and used without further purification. Melting points were measured on a Electrothermal-9100 apparatus and are uncorrected.

Preparation of sulfonated polyethylene glycol 1500 (PEG–SO_3H):

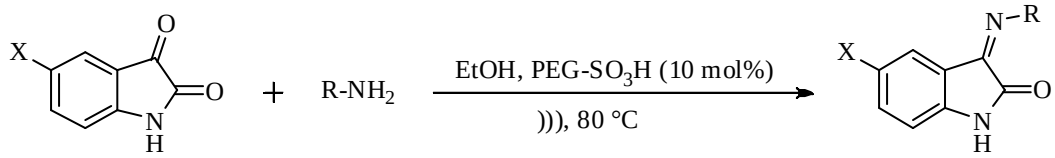
At 0 ˚C, chlorosulfonic acid (10 mmol) was added to a solution of PEG-1500 (1 mmol) in CH_2Cl_2 (10 mL), and the resulting solution was stirred at room temperature overnight. Then, the solution was concentrated under vacuum, and ether was added to it. The resulting precipitate was filtered and washed with ether three times to afford PEG–SO_3H as a gummy solid [19].

General procedure for the preparation of Schiff and Mannich bases of isatin derivatives and isatin hydrazones (3a-s):

A mixture of cyclic is at in derivatives **1a-c** (2 mmol), amines **2a-f** or hyrazines **2g-I** or thiosemicarbazide **2j** or semicarbazide **2k** (2 mmol), and PEG–SO_3H (10 mol%) in ethanol (10 mL) was irradiated at 80 ˚C for the time reported in Table **2** (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as an eluent). After completion of the reaction, the reaction mixture was poured into ice-cold water; the crude product was filtered and dried.

RESULTS AND DISCUSSION

Schiff and Mannich bases of is at in derivatives and is at in hydrazones prepared using condensation reaction of amines, hyrazines, thiosemicarbazide and semicarbazide with is at in derivatives [22]. Although, many reported methods are effective enough, low yields, long reaction times and hazardous conditions make it less favorable. Therefore, the introduction of a mild, simple, efficient and environmentally benign method to synthesize these compounds is still needed. In order to synthesis Schiff and Mannich bases of is at in derivatives and is at in hydrazones we have investigated reaction of amines, hyrazines, thiosemicarbazide and semicarbazide with is at in derivatives in EtOH, in the presence of catalytic amounts of PEG–SO_3H by using ultrasound



1a-c **2a-k** **3a-s**

irradiation (Scheme **1**).

Scheme 1. Synthesis of Schiff and Mannich bases of is at in derivatives and isatin hydrazones

To optimize the reaction conditions, the reaction between is at in **1a** and aniline **2a** was selected as a model reaction. When reaction was carried out in the presence of PEG–SO_3H (10 mol%), in

ethanol, under ultrasound irradiation and at 80 ˚C, the 3-(phenylimino)indolin-2-one **3a** was obtained in 93 % yield within 4 min. This reaction was also carried out in different solvents such as ethyl acetate, chloroform and acetonitrile, and the best results in terms of reaction time and yield of the preferred product **3a**, was obtained when the reaction was conducted in ethanol (Table **1**, entries 1-4). Decreasing the catalyst loading from 10 to 4 mol% significantly lowered the yield of the reaction (Table **1**, entries 5-7). The best catalyst loading was found in 10 mol%, which gave an excellent yield of **3a** after only 4 min. It is worth mentioning that the reaction temperature was optimized to 80 ˚C in ethanol (Table **1**, entries 8-10).

Table 1: Optimization of the model reaction between isatin 1a and aniline 2a

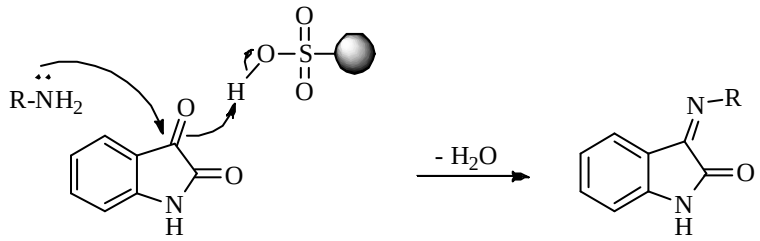
Entry	Solvent	Catalyst (mol %)	Temperature (˚C)	Time (min)	Yield (%)
1	EtOH	10	80	4	93
2	CH_3CN	10	80	22	85
3	$CH_3COOCH_2CH_3$	10	80	25	83
4	$CHCl_3$	10	80	35	78
5	EtOH	8	80	8	90
6	EtOH	6	80	12	87
7	EtOH	4	80	15	82
8	EtOH	10	65	15	88
9	EtOH	10	50	18	85
10	EtOH	10	r.t.	22	80

Based on the findings, we decided to apply this method for synthesis of Schiff and Mannich bases of isatin derivatives and isatin hydrazones, using condensation reaction of amines, hyrazines, thiosemicarbazide and semicarbazide with isatin derivatives under ultrasound irradiation and in the presence of PEG–SO_3H (Table **2**).

Table 2: Condensation reaction of isatin derivatives 1a-c with amines 2a-f, hyrazines 2g-i, thiosemicarbazide 2j and semicarbazide 2k

Compd. No.	X	R	Time (min)	Yield (%)	M.P. observed (°C)	M. P. reported (°C)
3a	H	C_6H_5	4	93	218-219	218 [22a]
3b	H	4-Cl-C_6H_4	6	90	239	240 [22b]
3c	H	4-Br-C_6H_4	5	91	236-238	239 [22b]
3d	H	4-CH_3-C_6H_4	4	94	220-221	222 [22b]
3e	H	4-CH_3O-C_6H_4	3	95	225	226 [22b]
3f	H	1-naphthyl	5	92	233	235 [22b]
3g	H	NH_2	6	91	218-220	221 [22c]
3h	H	C_6H_5-NH	7	90	200	202 [22c]
3i	H	2,4-NO_2-C_6H_3-NH	10	87	219-220	220 [22c]
3j	H	NH_2-CS-NH	6	91	196-198	199 [22c]
3k	H	NH_2-CO-NH	7	90	237	239 [22c]
3l	Cl	4-Cl-C_6H_4	7	89	242-243	244 [22b]
3m	Cl	4-Br-C_6H_4	6	90	231-233	234 [22b]
3n	Cl	4-CH_3-C_6H_4	5	92	199-201	202 [22b]
3o	Cl	4-CH_3O-C_6H_4	4	93	252	254 [22b]
3p	Cl	1-naphthyl	7	91	217	219 [22b]
3q	Cl	NH_2-CS-NH	7	90	209-211	212 [22b]
3r	Br	4-CH_3O-C_6H_4	4	94	261-262	264 [22b]
3s	Br	1-naphthyl	7	92	220	222 [22b]

A probable mechanism for the formation of the product 3 is presented in Scheme 2. The nucleophilic attack of the NH_2 group of the amines, hyrazines and (thio)semicarbazide on the carbonyl group of isatin is enhanced by PEG–SO_3H, because of the polarization of the π-electron cloud carbonyl group of isatin.



Scheme 2. A probable mechanism for the formation of Schiff and Mannich bases of isatin derivatives and isatin hydrazones

CONCLUSION

In summary, we have reported an efficient method for condensation reaction of isatin derivatives with amines, hyrazines, thiosemicarbazide and semicarbazide which leads to the synthesis of Schiff and Mannich bases of isatin derivatives and isatin hydrazones. These reactions was carried out in the presence of PEG–SO_3H (10 mol%), in ethanol, by using ultrasound irradiation at 80 ˚C. The procedure offers several advantages including high yield with short reaction time, clean reaction conditions in comparison with existing methods and do not need any further purification steps, which makes it a useful practical process for the synthesis of these compounds.

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