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Tetramethylguanidiniumtriflate catalyzed Henry reaction of isatins: An efficient synthesis of 3-hydroxy-3-(nitromethyl)indolin-2-one derivatives and their anti-diabetic activity

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ABSTRACT

The ionic liquid, *N,N,N,N*-tetramethylguanidiniumtriflate (TMGTf) was found to be an efficient catalyst solvent for Henry reaction between nitromethane and isatin derivatives to provide 3-hydroxy-3-(nitromethyl)indolin-2-one under mild conditions. The ionic liquid amenable to successive recycling without appreciable decrease in activity. Synthesized compounds have been screened for their anti-diabetic activity.

Keywords*: Ionic Liquid, Henry Reaction, Oxindole, Isatin.*

1. Introduction

Isatin is a privilaged lead molecule for designing potential bioactive agents, and its derivatives were reported to possess a broad spectrum of bioactivity as many of which were assessed anti-HIV [1], antiviral [2], anti-tumor [3], antifungal [4] and anti-angiogenic [5]. These interesting properties prompted much efforts toward the synthesis and pharmacological screening of isatin derivatives. During these investigations indolin-2-one (oxindole) moiety have been recognized as a biologically active framework [5-6]. Oxindole is an integral constituent of many natural products [7]. These compounds are found to be potent aldose reductase inhibitors (ARIs), which help to treat and prevent diabetic complications arising from elevated levels of sorbitol [8].

Thus, it is not surprising that access to several members of this class may be the goal of many research laboratories using new catalytic methods. In particular, the 3-substituted 3-hydoxyindolin-2-one moiety is present in a number of biological active alkaloids such as donwelwitindolinone C (Scheme 1), convolutamydines, SM-130686, in addition to several others [9].

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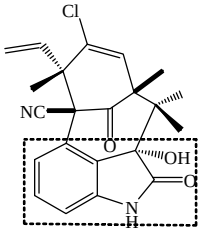
It is well known that 3-Hydroxy-3-nitromethyl-1,3-dihydro-indolin-2-one, an important intermediate for the synthesis of natural products, has been synthesized by Henry reaction [10]. The Henry reaction is an important carbon–carbon bond forming reaction having wide synthetic applications. In this reaction, a coupling reaction between a carbonyl compound and an alkylnitro compound takes place with the help of a basic organic, inorganic catalyst, quaternary ammonium salts and organic solvents under different reaction conditions. These aspects are summarized by Luzzio [10].

The nitromethyl adduct is valuable buliding block for the total synthesis of natural products and their analogues because the nitro functionality can easily be transformed into activity of functional groups, such as amine, ketone, nitrile oxide, carboxylic acid, hydrogen



Scheme 1. Structure of donwelwitindolinone C.

and so on [11]. Furthermore, asymmetric Henry reaction of isatins offers direct centry to the chiral 3-substituted-3-hydroxyoxindole [12].

Therefore, preparation of this heterocyclic nucleus has gained great importance in organic synthesis.

To the best of our knowledge, there are several reports in literature on the synthesis of 3-Hydroxy-3-nitromethyl-1,3-indolin-2-one derivatives. Conn and Lindwall have reported the synthesis of these compunds an ethanol solution using dimethylamine [13]. The use of strang organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), as a catalyst, did not improve the yield of reaction [14]. Meshram et al has reported (DABCO) an effcient catalyst for henry reaction in ambient temperature and solvent free conditions and also reported 3-hydroxy-3-nitroalkyl)-2-oxindole can be created by the reaction of isatins with nitroalkanes in *N,N*-dimethylformamide (DMF) under anhydrous conditions [15-16]. Elinson and co-workers undertook an electrolytic procedure to afford similar syntheses at ambient temperature [17].

Ionic liquids, by virtue of their organic and ionic nature, are potent solvents, exerting nearly all kinds of interactions on reacting species, including transition states, whereupon sometimes give rise to improved yields and rate enhancements [18]. Structural variation of ionic liquids gives more flexibility to their applications, as provides fine tunning of their miscibility to merit phase-separation from products [18].

Although each of the recent methods has merit, some methods are weakened by at least one limitation such as low yields, complicated workup procedure, requiring large amounts of organic solvents for chromatographic separation, and technical intricacy.

Therefore the development of a simple and efficient method, addressing the management of the above mentioned drawbacks, for the synthesis of 3-hydroxy-3-(nitromethyl)indolin-2-one derivatives would be an interesting challenge.

2. Experimental

2.1. General

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. IR spectra were recorded using a Shimadzu IR-470 spectrometer with KBr plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-500 MHz spectrometer.

2.2. General procedure

A mixture of isatin deivatives **1** (1 mmol) nitromethane **2** (3 ml), was added to a vial containing a magnetic stirring bar and 1 mL of the ionic liquid (TMGTf). The reaction mixture was sealed and stirred at room temperature until disappearance of the starting materials (5-7 min) (see Table 2). Then, the product was separate by filtration. In order to extract the ionic liquid, the residue was washed with 2 × 10 mL of water. The solid residue was recrystallized from ethanol (95.5%) to obtain pure product **3**. The ionic liquid was recovered from the aqueous extracts by evaporating of water in reduced pressure and then subjected to the next run with the same substrates. Table 3 displays similar high conversions obtained after consecutive recycling of the ionic liquid.

Selected spectral data

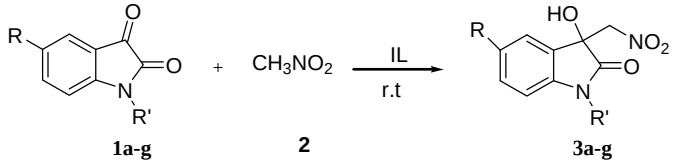
*3-hydroxy-5-methoxy-3-(nitromethyl)indolin-2-one (**3a**)*:

IR (KBr): $\bar{\nu}$ = 3300 (OH), 3200 (NH), 1730 (CO), 1550, 1300 (NO_2) cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ= 3.64 (3H, s, OCH_3), 4.74 (1H, d, $^{2}J_{HH}$= 12.71, CH_2), 4.80 (1H, d, $^{2}J_{HH}$= 12.71 Hz, CH_2), 5.82 (1H, br s, OH), 6.65-6.68. (2H, m, 2CH), 6.87 (1H, d, *J*= 1.99 Hz, CH), 9.73 (1H, s, NH) ppm. ^{13}CNMR (125 MHz, $CDCl_3$): δ= 56.1 (OCH_3), 74.0 (CH_2), 79.0 (C-OH), 111.5, 111.7, 115.7 (3CH), 128.7 (1C), 135.9 (C-N), 156.0 (C-OCH_3), 176.7 (C=O) ppm. Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C 50.42, H 4.23, N 11.76; Found: C 49.84, H 4.26, N 11.73.

3. Results and Discussion

Recently, guanidine-based ILs were synthesized [19]. In this work, we used guanidine-based ILs, 1,1,3,3-tetramethylguanidinium (TMG) triflate (TMGTf) prepared by neutralizing TMG with trifluoroacetic acid. With this background in mind and in line with our interest in the synthesis of oxindole compounds [20], we report herein an efficient and environmentally benign protocol for the synthesis of oxindole motifs compounds by condensation of isatin derivatives **1** and nitromethane **2** using ionic liquid (TMGTf) as solvent and catalyst.

The products were obtained in high yields by a simple work-up (Scheme 2).



Scheme 2. The model Reaction.

In order to optimize the reaction conditions, the condensation of 5-methoxy isatin **1a** (1.0 mmol), with nitromethane **2** (3.0 mmol), was attempted in different ionic liquids at room temperature. As can be seen from Table 1, the best results in terms of reaction time and yield were obtained in the basic ionic liquid TMGTf, at ambient temperature (entry 4). We examined the method with a range of substrates to determine the reaction specificity and scope. Consequently, various substituted isatins **1a-g** were used to react with nitromethane **2** under the optimized conditions (Table 2). From the results shown in Table 2, it is evident that both electron-deficient and electron-rich isatins afford fairly high yields of the desired oxindoles in a few minutes at ambient temperature. The known products have physical data consistent with those reported in literatures as well as the authentic samples prepared from previous reported methods. The structure of new compound 3a was confirmed by IR, ^{1}H, $^{13}CNMR$ and CHN. The next phase of our studies dealt with investigating the recyclability of TMGTf for the model reaction synthesizing 3a. As shown in Table 3, the ionic liquid can be reused without any significant loss of its catalytic activity after four runs.

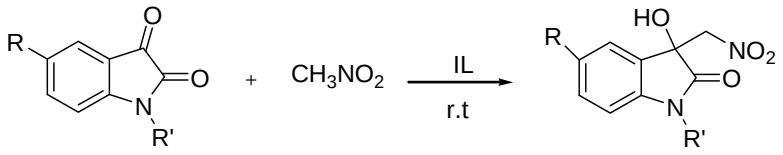
Table 1. Optimization of the reaction conditions.[a]

Entry	Catalyst	Time (min)	Yield[b] (%)
1	---	300	Trace
2	$[BMIm]BF_4$	60	Trace
3	[BMIm]Br	60	Trace
4	TMGTf	5	90
5	TMGT	15	Trace
6	$[HMIm]/HSO_4$	35	Trace

[a]Reaction conditions: 5-methoxyisatin **1a** (1.0 mmol), nitromethane **2** (3.0 mmol), TMGTf (1mL), room temperature.

[b]Isolated yields.

Table 2. Synthesis of oxindole motifs derivatives 3a-g in the presence of TMGTf.[a]



1a-g **2** **3a-g**

Product	R	R′	Time(min)	Yield(%)[b]	m.p. (°C)		Ref.
					Found	Reported	
3a	OCH_3	H	5	90	176-178	–	-
3b	H	H	5	86	148-150	146-148	[13,15,17]
3c	Br	H	7	92	162-164	163-165	[15,17]
3d	F	H	7	92	163-165	161-163	[17]
3e	I	H	5	90	276-278	274-276	[17]
3f	Br	Bn	5	91	123-125	121-123	[17]
3g	H	Ph	5	91	101-103	99-101	[15,17]

[a]Reaction conditions: Isatin derivatives 1a-g (1.0 mmol), nitromethane 2 (3.0 mmol), TMGTf (1mL), room temperature.
[b]Isolated yield.

Table 3. Recycling of TMGTf for the synthesis of 3a.[a]

Entry	Cycle	Yield (%)[b]
1	Fresh	90
2	First recycle	90
3	Second recycle	85
4	Third recycle	82

[a]Reaction conditions: 5-methoxyisatin **1a** (1.0 mmol), nitromethane **2** (3.0 mmol), TMGTf (1mL), room temperature.
[b]Isolated yield.

4. Antidiabetic Screening

4.1. Material and methods:

In this study adult male Wistar rats (220±30 g) were used. The rats were randomly divided to: controls, diabetic control (STZ), and treated diabetic animals by 3-hydroxy-3-(nitromethyl)indolin-2-one derivatives (3a – 3g) (10, 50 mg/kg).

4.2. Diabetic animals

Diabetes was induced by a single dose of streptozotocin STZ (60mg/kg) intraperitoneally [21]. 72 hr after STZ administration, blood was taken from lateral veins of the tail. After confirming the rise in blood glucose by glucometer

(Bionime rightest GM110 KMT, Switzerland), blood glucose levels of above 200 mg/dl were considered the basis for diabetes [22].

4.3. Preparation of 3-hydroxy-3-(nitromethyl)indolin-2-one derivatives

3-hydroxy-3-(nitromethyl)indolin-2-one derivatives (3a-3g) was solved in normal saline. Rats were anesthetized and blood samples were collected from the heart (Table 4).

4. Conclusions

In summary, an efficient method for the synthesis of oxindole system by using simple and readily available starting materials under catalysis of the ionic liquid, TMGTf, was introduced here. The ionic liquid acts as a catalyst solvent and can be recovered and reused for four times. Another advantages of the present method may be; requiring no metal catalysts or additional solvent and proceeding with appropriate rate respect to the methods that gave similar skeleton. On the basis of the biological evaluation, Synthesized compounds have been decreased the blood glucose.

Table 4. Effect of 3-hydroxy-3-(nitromethyl)indolin-2-one derivatives on blood glucose, treated diabetic groups compared to untreated diabetic group and control, Mean± SEM[a]

Compounds	Blood glucose (mg/dl)	
	(STZ+10mg/kg)	(STZ +50 mg/kg)
3a	161.5±3.1# # #	150.7±3.4# # #
3b	165.2±7.6# # #	155.2±6.6# # #
3c	166±11.5#	118±8 # #
3d	193±27# # #	259±8.9
3e	143±14.8#	126.7±6.3##
3f	111.1+16.2# #	142.85±12.7#
3g	156±0.2# # #	157.2±0.7# # #
Controls (not diabetic)	84.1±3.3	
Diabetic control (STZ, diabetic)	321.7±12***	

[a]Significant compared to the normal control #: Significant compared to the diabetic control(One-way ANOVA-Post Hoc LSD test, n=7, #, P<0.05, ##, P<0.01, ###, ***P<0.001)

Acknowledgment

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