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ARTICLE TYPE

"On water" Catalysis: An expeditious approach for the synthesis of Quaternary Centered 3-hydroxy-3-(nitromethyl)indolin-2-one derivatives

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A novel efficient, eco-friendly method "on water" has been developed for Henry reaction of isatins with nitro methane to afford 3-hydroxy-3-nitromethylindolin-2-ones. An enhancement in reaction rate was observed "on water" under mild and catalyst-free conditions. This reaction tolerated a wide range of substrates with good to excellent yields of the product and even applicable in large-scale. Moreover this method is advantageous with regard to green aspects, in terms of reducing the waste generated by using toxic solvents.

Water has a significant role as it is universal medium for all chemical reactions of life.[1] Organic reactions conceded 'On-water' have become one of the most intriguing area of research in green chemistry.[2] Recent progress is initiated in developing efficient catalytic processes in aqueous-phase which allows insight into Nature's way of chemical synthesis tend to be an important challenge for organic chemists to be tackled.[3] Indeed, to maintain ecological factors there is a need to reduce the amount of toxic and hazardous substances arising from constant usage of solvents in synthetic pathways is of considerable significance.[4] In view of this, water as a solvent for catalysis is desirable as it is economical, non-toxic and environmentally attractive medium.[5] The major breakthrough for water as a reaction medium comes from the studies done by Breslow in 1980s.[6] The subsequent exploration to describe the substantial rate acceleration for insoluble reactants, termed as "on-water" catalysis by Sharpless and co-workers, have attracted the attension of organic chemists towards aqueous media.[7] The replacement of catalysts and hazardous solvents with relatively benign solvents such as aqueous reaction medium, catalyst-free and high atom economy, is one of the most essential contributions for an ideal green synthesis.[8] Recently, the development of green protocols for the synthesis of highly functionalized bio-active motifs has emerged as an attractive area of research.[9]

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Oxindoles, with quaternary centre at C-3 position constitute a common structural moiety for several drug candidates and bioactive natural products.[10] In particular 3-substituted-3-hydroxyoxindoles is an emerging new scaffold for drug discovery with a broad spectrum of biological activities.[11] Several pharmacologically active alkaloids such as dioxibrassinine, CPC-1, Donaxaridine, Maremycin A and B, Horsfiline, spirobrassinin in addition to several others contain 3-hydroxyoxindole moiety[12] as shown in (Figure 1).

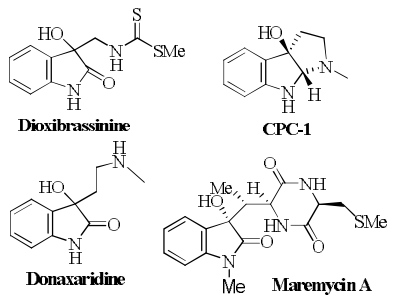
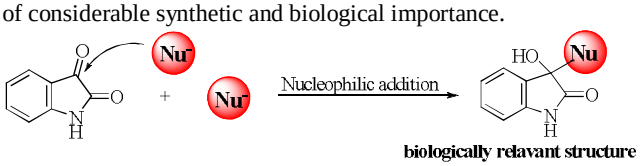


Fig. 1 Natural products containing the 3-hydroxyindol-2-one scaffold.

The nucleophilic addition reaction to isatins is the most straightforward approach for direct entry of 3-substituted 3-hydroxyoxindole framework (Scheme 1). Significant efforts has been focussed on the development of efficient methods for the construction of functionalized frameworks with this structure is of considerable synthetic and biological importance.



Scheme 1 Synthesis of 3-substituted-3-hydroxyoxindoles

The nucleophilic addition of nitroalkanes to various electrophiles, especially carbonyl compounds, is one of the most important approaches to form C–C bonds.[13] We explored Henry (nitroaldol) reaction of isatins with nitroalkanes, affording β-nitroalcohols, potential synthons for the synthesis of complex natural products. The so obtained Henry adduct **3a** can serve as synthetic precursor for natural products like dioxibrassinin and spirobrassinin which

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exhibits various biological properties including antifungal, antitumor as well as oviposition stimulation (Figure 2).[14]

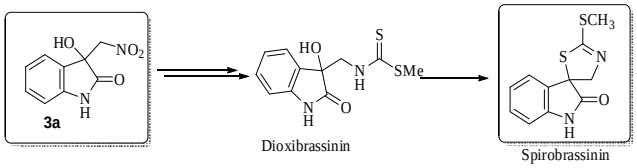
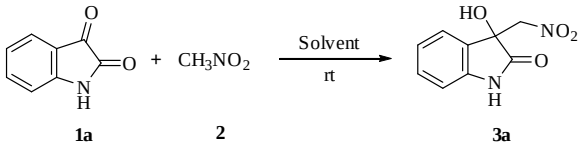


Fig:2 Representative examples showing the synthetic importance of Henry adduct **3a**

The condensation of nitromethane with isatin has been reported using diethylamine ethanol solution, DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) and DABCO (1,4-Diazabicyclo[2.2.2]octane) as bases for the formation of adduct.[15] All the existing methods for Henry reaction with cyclic ketones such as isatins inevitably required a base, by which there will be a great difficulty in the recovery of pure product as under strong basic conditions there is a every possibility of rearrangement of the product. The developed methods suffer from limitations such as tedious work-up, longer reaction time, unsatisfactory yields and narrow scope of substrates. In view of this, there is still need to develop a generally applicable method for the synthesis of functionalized 3-hydroxy-3-(nitromethyl)indolin-2-ones. Nevertheless, organic synthesis involving nucleophilic addition of nitromethane to isatins under the "on water" conditions remains elusive.

In continuation of our interest to develop green synthesis protocols for C3 functionalisation of isatins with quaternary centres,[16] we reported the enantioselective synthesis of 3-hydroxy-3-nitromethyl indolin-2-ones.[17] During our work for preparation of their respective racemic products we observed the formation of henry adducts by Click-chemistry approach under on-water conditions due to the fact that the highly reactive β-carbonyl group of the isatin derivatives is very susceptible to nucleophilic attack. Herein, we report a clean, an atom economical, catalyst-free, very simple and highly efficient strategy for henry reaction of isatins to give the addition products in excellent yields at room temperature. In practical terms, the catalytic "on water" process through the activation of alkane C–H bond provided an environmentally benign and highly efficient approach for the synthesis of 3-hydroxy-3-nitromethyl indolin-2-ones.

To investigate the feasibility of "on water" catalytic route for synthesis of 3-hydroxy-3-nitromethyl indolin-2-one, sequence of experiments were carried out using **1a** with **2** as a model reaction. Subsequently, the solvent effect on the reaction was examined using various organic solvents (Table 1). When the reaction was performed in DMF, MeOH, DMSO and $CHCl_3$ lower yields of Henry product **(3a)** were obtained (entry 4, 6, 8 and 9). Whereas in *iso*-propanol, THF, DCM and acetonitrile, only trace amounts of Henry adduct **(3a)** was formed (entry 3, 5, 7 and 10). However, when the reaction was carried out without any solvent and toluene, product formation was not observed (entries 2 and 11). All the solvents screened gave low yields of the desired product albeit in long reaction times. In contrast, water showed significant improvement over the other solvents in terms of yield and reaction time (entry 1). To our delight water found to be the best system to afford Henry adduct in excellent yields within 30 min at room temperature under vigorous stirring.



Scheme 2. Henry reaction of isatin with nitroalkane.

Table 1. Solvent effect on the yield of Henry reaction of isatin[a]

Entry	Solvent	Time (h)	Conversion [%]
1	water	0.5	98
2	neat	72	-
3	IPA	72	10
4	DMF	60	40
5	THF	72	20
6	MEOH	60	30
7	DCM	72	10
8	DMSO	72	30
9	$CHCl_3$	72	30
10	CH_3CN	72	20
11	Toluene	72	-

[a]All reactions were performed using isatin (0.5 mmol), nitro methane (2 equiv) and solvent (2 mL) at room temperature

The rate of acceleration of reaction "on-water'' is due to the formation of hydrogen bonds on the interface.[18] Also the amount of water is found to be crucial in determining the rates of reaction and yields of the product. When 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 mL of water was taken, **3a** was obtained in 60%, 96%, 98%, 99%, 92% and 90% yields within 72h, 3h, 1h, 0.5h, 6h and 6h successively. With 4 mL of water the yield slightly decreased to 92%. Further increase in water content, there is considerable reduction in yield due to dispersion of the reagents. The best result was obtained in the presence of 3.0 mL of water with 99% yield, within 0.5 h of reaction time (Fig. 3).

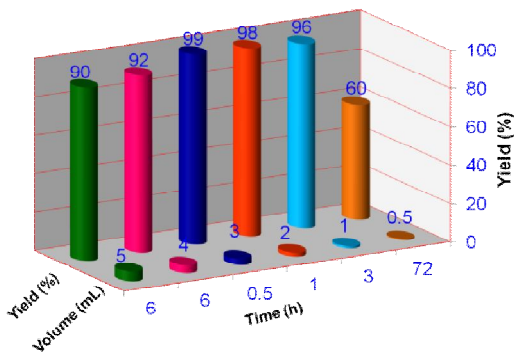


Figure. 3 Effect of volume of water on the yield and reaction time of 3-hydroxy-3-nitromethyl indolin-2-one (**3a**)

The reaction was examined with distilled, HPLC grade as well as in tap water. However similar results were obtained as obtained with tap water (entry 1, Table 1). No considerable difference was observed in terms of yield. Paying attention to the need to develop economical sustainable methods we carried out all reactions in tap water. As the reaction proceeds in tap water also we examined the role of pH of water for product formation. The

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maximum yield of the product was obtained at a pH of 7.95 and low yield at pH of 6.0 (Fig. 4).

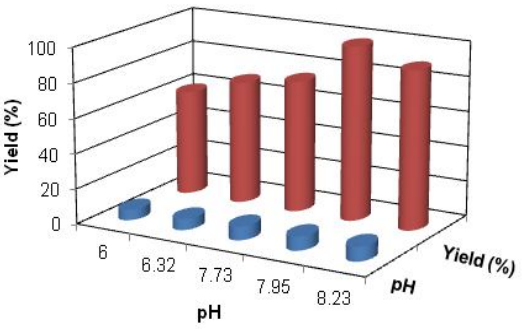
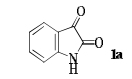
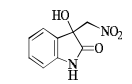
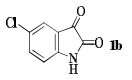
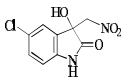
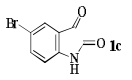
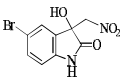
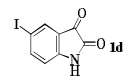
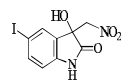
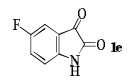
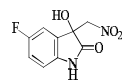
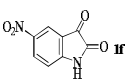
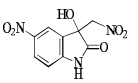
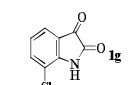
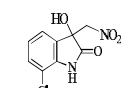
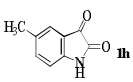
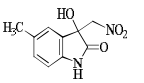
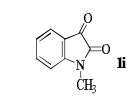
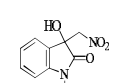
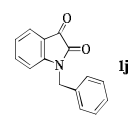
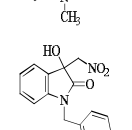
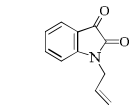
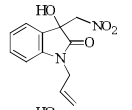
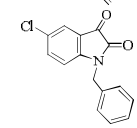
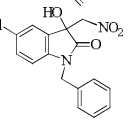
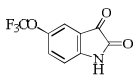
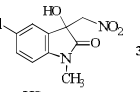
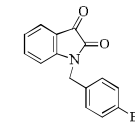
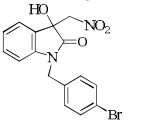
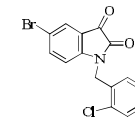
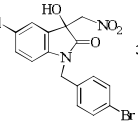
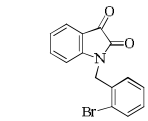
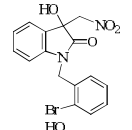
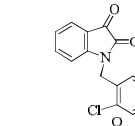
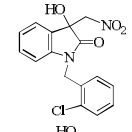
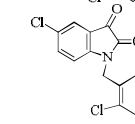
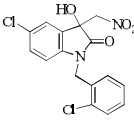


Figure. 4 Effect of pH on the yield of 3-hydroxy-3-nitromethyl indolin-2-one (**3a**)

Having established the optimal reaction conditions, the scope of the reaction was extended to isatin bearing different substituents at 5-position and methyl, allyl, benzyl substituents at the N-1 position. The results are summarized in Table 2. All the substrates afforded the desired products with excellent yields (74-99%) at room temperature in aqueous medium.

Table 2. Catalyst-free Henry reaction of isatin on water.[a]

Entry	isatin	product	Time (h)[b]	yield [%][c]
1	 **1a**	 **3a**	0.5	99
2	 **1b**	 **3b**	24	90
3	 **1c**	 **3c**	11	94
4	 **1d**	 **3d**	48	94
5	 **1e**	 **3e**	6	91
6	 **1f**	 **3f**	24	90
7	 **1g**	 **3g**	24	91
8	 **1h**	 **3h**	48	80
9	 **1i**	 **3i**	48	88
10	 **1j**	 **3j**	11	92
11	 **1k**	 **3k**	48	74
12	 **1l**	 **3l**	8	88
13	 **1m**	 **3m**	11	96
14	 **1n**	 **3n**	48	85
15	 **1o**	 **3o**	30	88
16	 **1p**	 **3p**	30	85
17	 **1q**	 **3q**	9	92
18	 **1r**	 **3r**	18	91

[a]Reaction conditions: Isatin (0.5 mmol), nitromethane (2.0 mmol) and water (3 ml) at room temperature. [b]Time in hours, [c]Overall yield of adducts.

Several N-alkylated isatins with substituents (methyl, benzyl, allyl, halo substituted benzyl) at N-1 position are synthesized by adapting the reported procedure and subjected to functionalisation at C-3 position. The reaction is fast with high yields with unsubstituted isatin when compared to substituted halogens at C-5 position (Table 2). In case of benzyl substituent at the N-1 position, the reaction proceeded faster with good yields than that of methyl and allyl group at the N-1 position (entries **3i, 3j** and **3k).** When N-allyl isatin is employed the reaction is comparatively slow with 74% yield of the product (entry **3k).** In case of N-methyl isatin and 5-methyl isatin, the reaction was slow with 80 and 88% yields respectively (entries **3i** and **3h)**. All examples of isatins with electron withdrawing groups at C-5 position, C-7 position and substituents at N-1 position lead to equally satisfying results.

The developed protocol was found to be successful not only with isatin having electron withdrawing but also with electron donating substituents. All the screened structurally varied N-substituted oxindole derivatives underwent efficient nitroaldol addition with good yields of Henry adducts in an aqueous reaction medium (Table 2). One of the most unique features of

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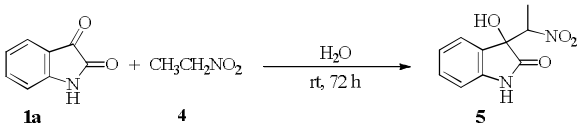
this nitroaldol reaction is that, it works "on water" under catalyst-free or additive-free reaction conditions.



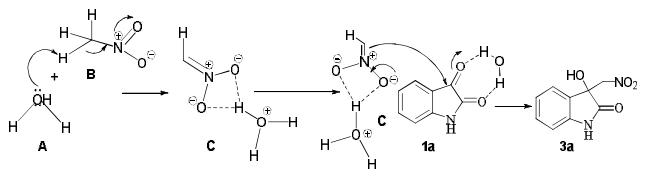
1a **4** **5**

Scheme 3. Henry reaction of isatin with nitroethane.

Further the reaction with nitroethane **4** and nitropropane has been performed. The desired product was observed for nitroethane in good yields (90%) with diastereomeric ratio (98:2) after 72 h as shown in scheme 3. In case of nitropropane, the reaction tends to be sluggish with very low yield (<10%) even after 96 h.

In order to demonstrate the scale-up potential of this efficient transformation, we conducted a gram-scale synthesis of **3a** (Scheme 2), wherein isatin **1a** (30 mmol, 4.41 g), nitromethane **2** (120 mmol, 6.4 mL) and 180 mL of tap water were taken. All the products were characterized by ^{1}H NMR,^{13}C NMR and mass spectroscopy.

On the basis of the above observations, a tentative mechanism to rationalize this transformation is illustrated in Scheme 4. The distinctive basicity, polarity and hydrogen bonding capacity of water makes it efficient for stabilizing isatin as well as nitroalkyl anion. We reasoned that, water work as a solvent as well as a mild base which abstract acidic α-hydrogen of nitroalkane and efficiently form nitroalkyl anion **C**. This nitroalkyl anion (azinate) attacks on highly reactive β-carbonyl group of isatin **1a** and form desired 3-hydroxy-3-(nitroalkyl)-2-oxindole product in high yield **3a.**



Scheme 4. Possible Reaction Mechanism

Conclusions

An eco-friendly and efficient method "on-water" has been developed for synthesis of 3-hydroxy-3-nitromethylindolin-2-one frameworks under catalyst-free conditions. It serves as invincible system for the production of Henry adducts from isatin, which involves water as solvent, no base, room temperature, with excellent yields of the desired products. The method has good level of generality and applicable for various substituted isatins under "on-water" conditions. The water after the reaction (after the filtration) contains only trace amount of nitromethane. The advantage of our reaction is base free reaction, as most of the bases are water soluble, which decreases the effort for the purification as water has high energy of evaporation**.** The new compounds reported herein could find potential application in synthetic chemistry.

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GRAPHICAL ABSTRACT

An efficient, eco-friendly method “on water” has been developed for Henry reaction of isatins with nitro methane to afford 3-hydroxy-3-nitromethylindolin-2-ones. An enhancement in reaction rate was observed “on water” under mild and catalyst-free conditions. This reaction tolerated a wide range of substrates with good to excellent yields of the product and even applicable in large-scale. Moreover this method is advantageous with regard to green aspects, in terms of reducing the waste generated by using toxic solvents.