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Graphical Abstract

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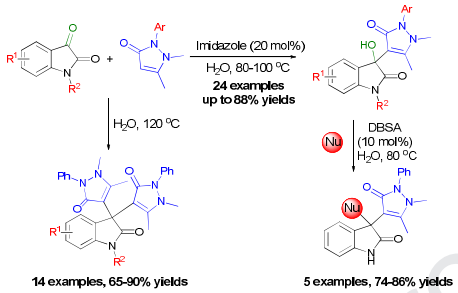

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ABSTRACT

The selective condensation of pyrazolones with isatins using water as the reaction medium is presented. This strategy provides an environmentally benign synthetic route to synthesize various potentially bioactive pyrazolone substituted oxindoles.

The discovery and development of environmentally benign protocols for the diversity-oriented synthesis of heterocyclic compounds is of great significance to chemical and pharmaceutical research.[1] Water, the solvent of choice for Nature, is cheaper, safer, and cleaner than conventional organic solvents.[2] In addition to being a green reaction medium, water has special physical and chemical properties, such as high heat capacity, high dielectric constant, amphoteric nature and extensive H-bonding ability.[3] These special properties allow chemists to realize reactivities and selectivities that cannot be achieved in common organic solvents.[4] Therefore, extensive efforts have focused on the use water as a reaction medium, and great success has been achieved in modern organic synthesis.[5] However, pursuing practical organic reactions in water for the synthesis of biologically relevant heterocycles is still in early stages and more research is needed.[6]

Pyrazolone, a unique five-membered heterocycle featuring two adjacent nitrogen atoms, is identified a significant pharmacophore because of its prevalence in bioactive natural alkaloids and pharmaceuticals.[7] In particular, antipyrine (1-phenyl-2,3-dimethylpyrazol-5-one) and its derivatives have been widely used for a long time in medicine as antipyretic, analgesic, sedative, antimicrobial, antiviral, antioxidant, anticancer, and anti-inflammatory drugs (Figure 1).[8] Thus, considerable attention has been directed towards the synthesis of antipyrine analogues for drug discovery.[9] Although several of methods, such as electrophilic substitutions[10] and metal-catalyzed C-H functionalization[11] have been used for the synthesis of antipyrine analogues, the existing synthetic routes to antipyrine-substituted alkanol products are limited to the nucleophilic addition of aldehyde with Grignard reagent and the reduction of the corresponding ketone.[12] These methods suffer from many disadvantages, such as narrow substrate tolerance, harsh reaction conditions and low atom economy. Theoretically, the direct nucleophilic addition of antipyrine to carbonyl compounds is the most convenient strategy for the construction of antipyrine-substituted alkanol products. However, to the best of our knowledge, no report was found in literature on the selective condensation of antipyrine with carbonyl compounds, and most of these reactions resulted in the formation of diantipyrine-substituted products.[13] Herein, we report that the selective condensation of *N*-substituted pyrazolones with isatins can be realized in water (Scheme 1).

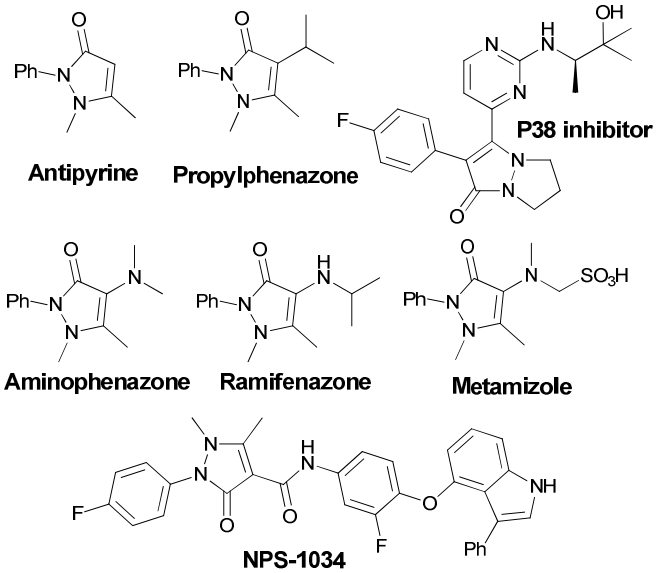
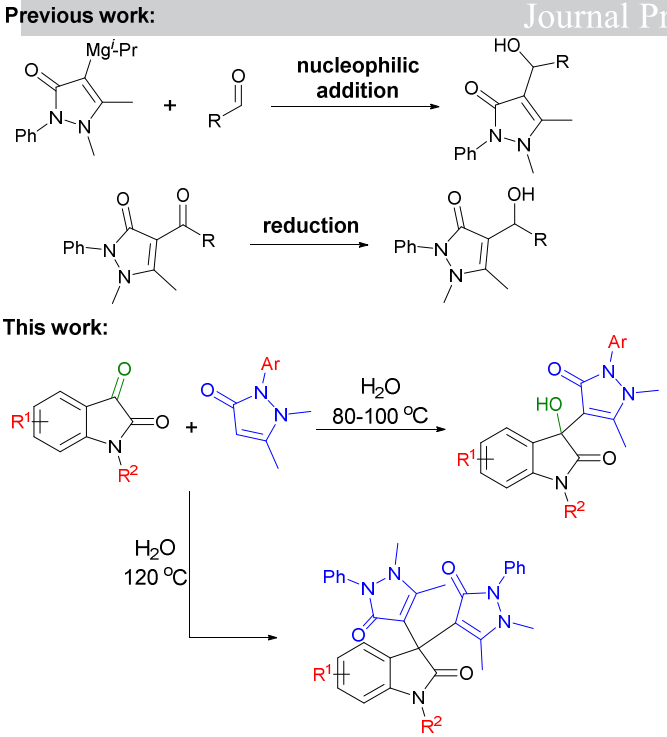


Figure 1 Examples of pharmaceutically active pyrazolones

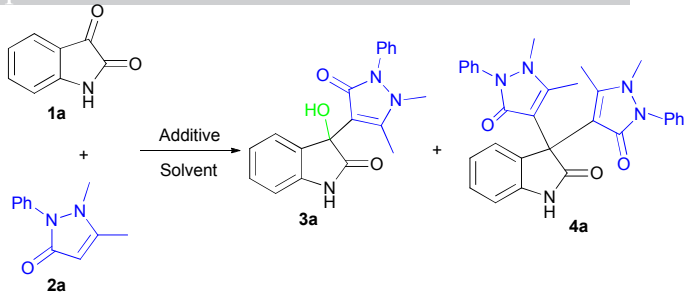


Scheme 1 Synthetic routes to pyrazolone-substituted alkanol products

Initially, we investigated the reaction of isatin with antipyrine, leading to the formation of 3-antipyrine substituted 3-hydroxy-2-oxindole, as a model for optimizing the reaction condition (Table 1). Different solvents including water, DMF, DMSO, Toluene, Dioxane, $CHCl_3$, MeOH and MeCN were studied at various temperatures. No product was formed when the reaction was performed at room temperature. Elevating the reaction temperature from rt to 65 °C, the desired product was obtained with 58% yield in water, while no product or only traces of product were observed in other organic solvents. Increasing the reaction temperature in water from 65 °C to 80 °C and further to 100 °C did not improve the yield of the desired product, but led to the formation of a further nucleophilic substitution product **4a** (*bis*-antipyrinyl oxindole). We speculated that the increased acidity of water at elevated temperature is the reason of further nucleophilic substitution process.[14] To suppress this competitive process, a series of base additives were then screened. To our delight, when 20 mol % imidazole was tested, it resulted in 86% of the 3-antipyrine substituted 3-hydroxy-2-oxindole product **3a**, and no *bis*-antipyrinyl oxindole product **4a** was observed. Other bases, such as $NaHCO_3$, K_2CO_3, DABCO, DMAP, DBU, Et_2NH and TMG, gave inferior results. When the amount of imidazole was reduced to 10 and 5 mol %, 10% and 20% of **4a** was isolated respectively in 48 h, which suggests the key role of imidazole for this protocol.

Having optimized the reaction conditions, we then examined the substrate scope of this nucleophilic addition reaction, and the results are shown in Table 2. The procedure serves as a general approach to structurally diverse product **3**. Various isatins and *N*-substituted pyrazolones could engage in the process, providing the corresponding products in moderate to good yields. Generally, the reaction worked well with electron-withdrawing groups on the 5-position of isatins, providing 3-antipyrine substituted 3-hydroxy-2-oxindole products in 60–82% yields, whereas electron-donating groups underwent moderate conversion into the products. 7-fluoro-, 7-chloro- and 7-bromo isatins reacted well with antipyrine in 29–48 h to furnish the desired products in 74–84% yields.

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Temp. [°C]	Additive	t [h]	3a Yield[%][b]	4a Yield[%][b]
1	Organic solvents	25	none	48	-	-
2	H_2O	25	none	48	-	-
3	H_2O	65	none	48	58	nd
4	DMF	65	none	48	-	-
5	DMSO	65	none	48	-	-
6	Toluene	65	none	48	-	-
7	Dioxane	65	none	48	-	-
8	$CHCl_3$	65	none	48	-	-
9	MeOH	65	none	48	trace	-
10	MeCN	65	none	48	trace	-
11	H_2O	80	none	48	55	21
12	H_2O	100	none	48	24	68
13	H_2O	80	$NaHCO_3$	48	37	8
14	H_2O	80	K_2CO_3	48	34	10
15	H_2O	80	DABCO	48	40	8
16	H_2O	80	DMAP	48	51	17
17	H_2O	80	DBU	48	65	9
18	H_2O	80	Et_2NH	48	46	18
19	H_2O	80	imidazole	48	86	-
20	H_2O	80	TMG	48	38	<5
21[c]	H_2O	80	imidazole	48	67	20
22[d]	H_2O	80	imidazole	48	73	10

[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **1**, 0.2 mmol of **2a** and 20 mol % additive in 1 mL water.

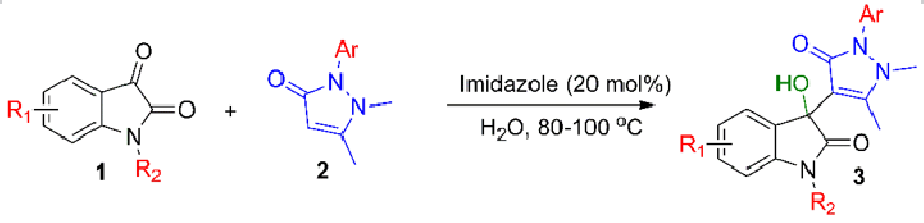
[b] Isolated yield.

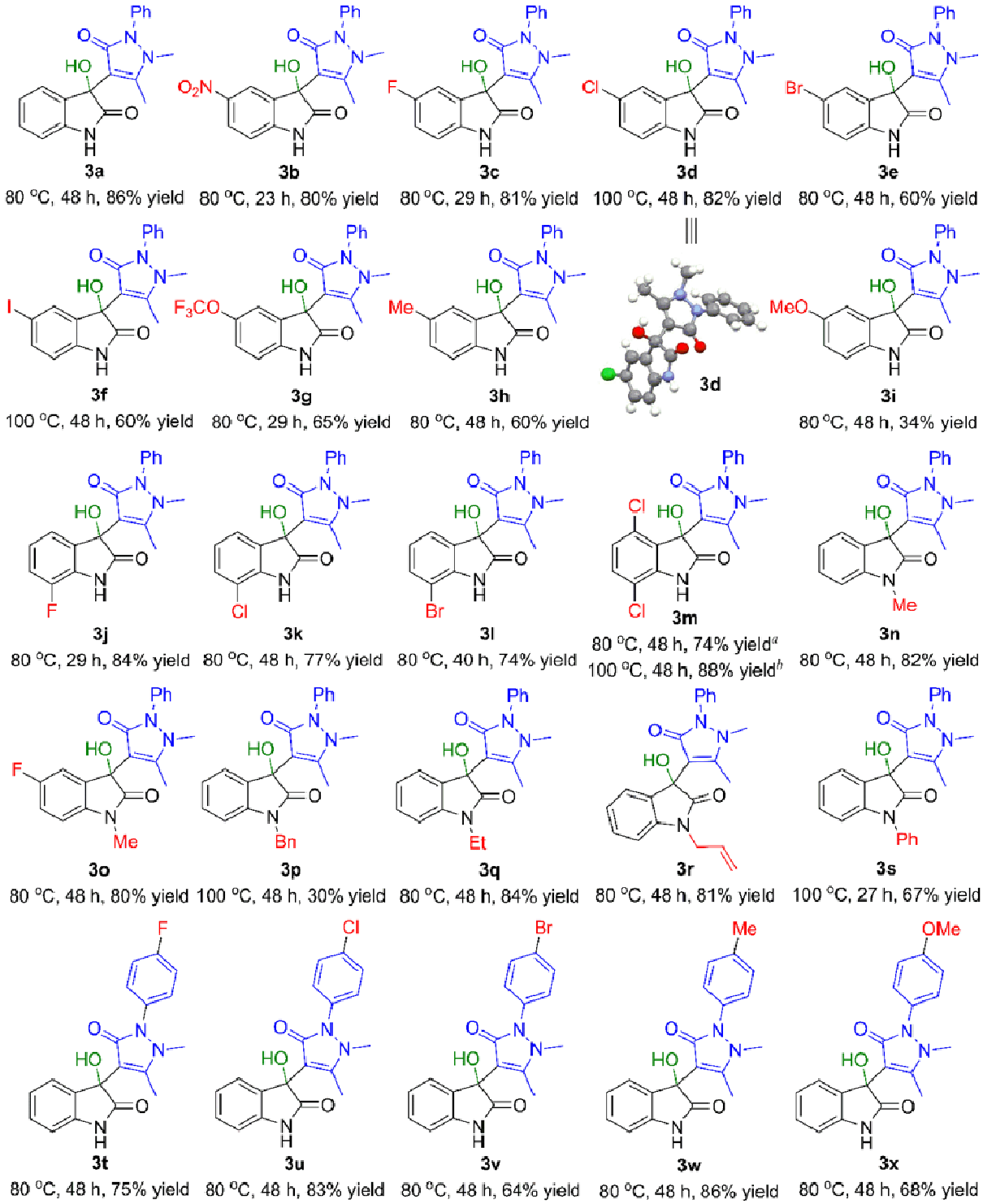
[c] 5 mol % of the catalyst was used.

[d] 10 mol % of the catalyst was used.

Interestingly, di-substituted isatin (4,7-dichloroisatin as an example) was also applicable for this reaction even in the absence of imidazole, affording the desired product **3m** in 88% yield. The scope of this nucleophilic addition reaction was further extended to *N*-protected isatins. It is shown that *N*-methyl isatins, *N*-ethyl isatin, *N*-allyl isatin and *N*-phenyl isatin were also compatible substrates with the formation of the corresponding products in 67–84% yields. However, poor result was obtained when *N*-benzyl isatin was employed, presumably due to its poor dispersibility in water. Moreover, it is recognized that the electronic nature of *N*-aryl substituted pyrazolones has no pronounced on the reaction yields. Pyrazolones with different groups, such as fluoro, chloro, bromo, methyl, and methoxyl were proceeded smoothly to afford the corresponding products (**3t**–**3x**) in moderate to good yields. However, almost no conversions were observed when the aryl group in **2** was replaced with methyl group or hydrogen atom. The structure of the product was unambiguously confirmed on the basis of single-crystal X-ray diffraction analysis of compound **3d**.[15]

Table 2 The substrate scope of direct nucleophilic addition reaction[a]

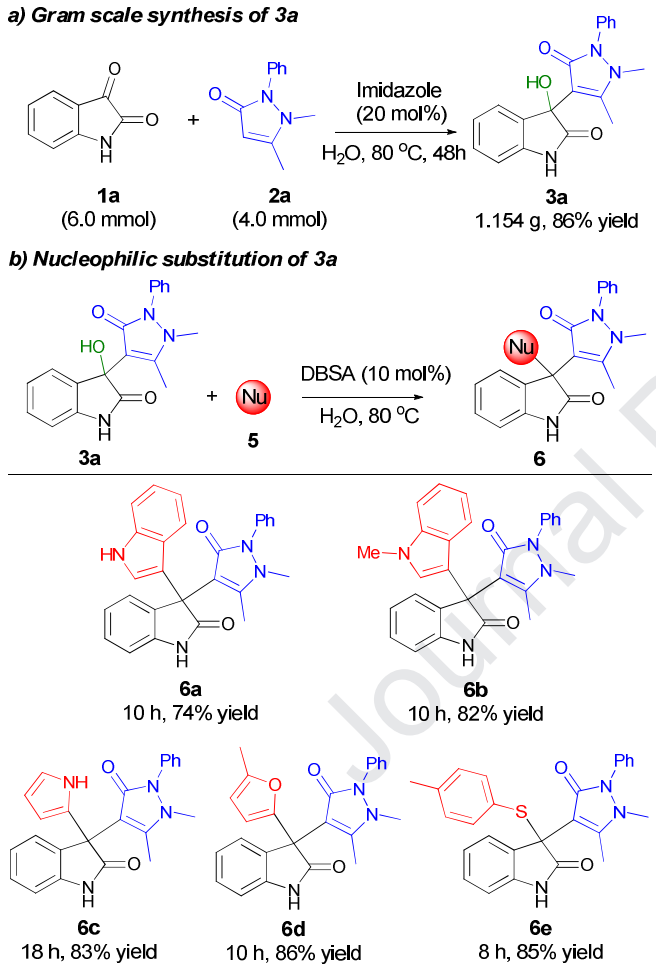




[a] Unless noted, reactions were performed with 0.4 mmol of **1** and 0.2 mmol of **2** in 1 mL water with 20 mol % imidazole as the catalyst. Yield refers to the isolated product.

[b] Without the addition of imidazole.

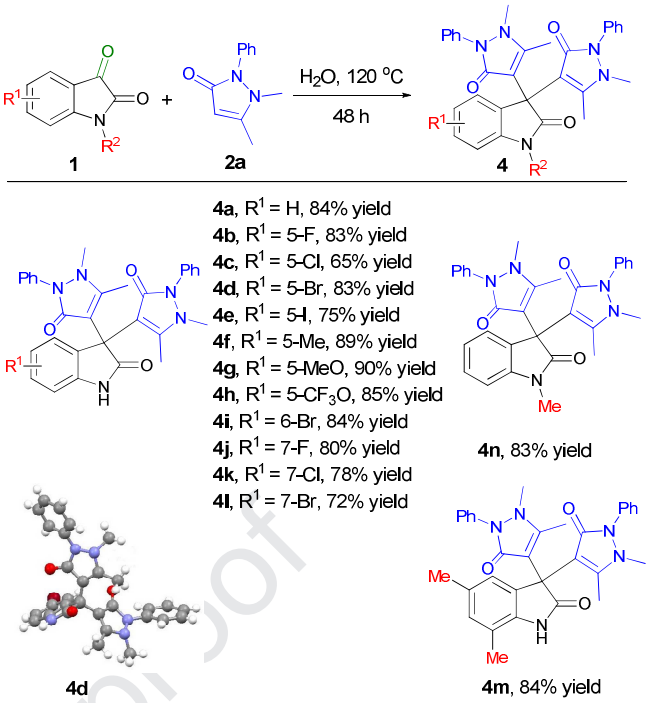
Most importantly, the present method could be used for preparative synthesis, as demonstrated by a scale up reaction using 6.0 mmol of **1a** and 4.0 mmol of **2a** under the similar reaction conditions described above. After completion of the reaction, the desired product **3a** (> 99% purity) was obtained in 1.154 grams with 86% yield by simple filtration and washing with water. (scheme 2a). This strategy provided a direct, step-economic and environmentally benign access to various 3-pyrazolone substituted 3-hydroxy-2-oxindole products with important biological.[16] Moreover, compound **3a** displays excellent synthetic application in diversity-oriented synthesis. As shown in scheme 2b, various nucleophiles such as indole, *N*-methyl indole, pyrrole, 2-methylfuran, and *p*-toluenethiol reacted well with **3a** in the presence of DBSA (4-Dodecylbenzenesulfonic acid) to furnish di-substituted 2-indolinones **6** in high yields.



Scheme 2 Synthetic utility of this "On water" process

In addition, without the addition of imidazole, the reaction between isatins with antipyrine resulted in the formation of di-antipyrine substituted oxindoles under high temperature (120 °C) water. As shown in Table 3, isatins with various substituents on the benzene ring were all found to be suitable for the reaction and gave **4a**–**4l** in 65–90% yields. Di-substituted isatin (5,7-dimethylisatin as an example) and N-methyl isatin were also well tolerated and afforded the target compounds with good yields. It should be noted that all of the desired products were isolated by simple filtration and does not require any column chromatographic purification. The structure of **4d** was confirmed by an X-ray crystallographic analysis.[15]

Table 3 Synthesis of 3,3-di-antipyrine substituted oxindoles[a]



[a] Unless noted, reactions were performed with 0.2 mmol of **1** and 0.45 mmol of **2a** in 1 mL water. Isolated yield by washing process.

In conclusion, the selective condensation of pyrazolones with isatins could be realized in water. Various mono-pyrazolone substituted 3-hydroxy oxindoles were achieved in the presence of imidazole under hot water condition (80–100 °C), while di-antipyrine substituted oxindoles were obtained under high temperature water condition (120 °C). This process provides a highly efficient and environmentally benign approach for the diversity-oriented synthesis of Antipyrine derivatives, a structural scaffold for various pharmaceutical agents.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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Highlights

The synthesis of both mono-antipyrine and di-antipyrine substituted oxindoles.

The selective condensation of pyrazolones with isatins in water.

Works well with a wide range isatins.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: