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# Noncatalytic on water aldol reaction of isatins with cyclic 1,3-diketones at room temperature without the need for subsequent chromatography

**Michail N. Elinson,* Yuliya E. Ryzhkova, Varvara M. Kalashnikova and Mikhail P. Egorov**

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: elinson@ioc.ac.ru*

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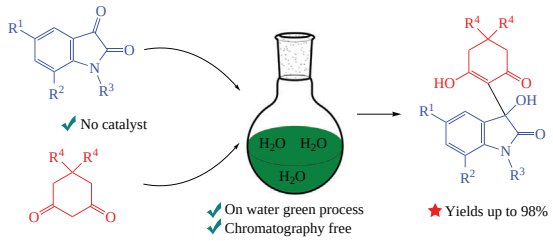
**Noncatalytic on water aldol transformation of isatins and cyclic 1,3-diketones results in substituted 3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-ones in 87–98% yields. Optimized conditions have been found and a mechanistic rationale for the reaction has been deduced. The new efficient and facile process represents a convenient way to compounds with the 3-hydroxyindolin-2-one and 3-hydroxycyclohex-2-en-1-one moieties.**




*Keywords*: aldol reaction, noncatalytic, on water, isatin, 1,3-diketone, 3-hydroxyindolin-2-one.

Water plays an essential role in biological and chemical processes, though its use as a solvent in organic synthesis is still limited.[1–3] It is known that certain organic reactions are accelerated in aqueous suspensions or emulsions,[4,5] the rates of these transformations being higher than those under solvent-free (neat) or homogeneous conditions.[6] The term 'on water reactions' was introduced[1,4–9] for these processes. In general, reactions in water as well as noncatalytic processes are promising for green chemistry and the ideal synthesis concept.[10]

Aldol reaction represents a classic carbon–carbon bond formation after nucleophilic addition of enolate to carbonyl group to form aldol as a unit occurring in many natural molecules and pharmaceuticals.[11–15] An example of the process of such type is Henry reaction, which involves base-catalyzed addition of nitroalkanes to aldehydes or ketones.[16–18] However, descriptions of the aldol reaction of cyclic 1,3-dicarbonyl compounds with carbonyl group are rare. There have been two pure chemical examples found, including an addition of dimedone to *N*-acetyl-2-aminobenzaldehyde in ethanol[19] and melting dimedone with piperonal[20] as well as one electrocatalytic process, namely the reaction of isatins with cyclic 1,3-diketones with formation of previously unknown substituted 2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)cyclohexane-1,3-diones in 70–85% yields described by our group.[21] The substituted 3-hydroxy-2-oxindole moiety is present in numerous natural products and pharmaceutically active compounds.[22–25]

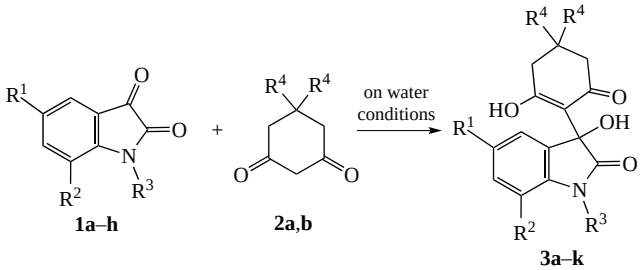
On the other hand, the substituted 3-hydroxycyclohex-2-en-1-one fragment is related with enzyme inhibition,[26,27] antioxidant, antiiflammatory and anticancer activities.[28–30]

In the last decade we have described noncatalytic reactions of carbonyl compounds and C–H acids[31–34] as well as catalyst-free on water processes of the same type.[35,36] Considering our results on the noncatalytic and on water transformations as well as the biomedical significance of substituted 3-hydroxy-2-oxindoles, we were prompted to design a convenient and facile methodology for synthesis of the 3-hydroxy-2-oxindole scaffold, which contains also the pharmacologically active 3-hydroxycyclohex-2-en-1-one moiety at the 3-position.

This work deals with facile, selective and efficient transformation of isatins **1a–h** and cyclohexane-1,3-diones **2a**,**b** into substituted 3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-ones **3a–k** (Scheme 1, Table 1). The procedure developed is consistent with eco-friendly green chemical processes with exclusion of organic solvents,[37,38] like solvent-free[39,40] and on water[7,41] reactions.

First, we explored reaction of isatin **1a** and 5,5-dimethylcyclohexane-1,3-dione **2a** under solvent-free conditions (see Table 1, entries 1–4) with no catalyst or in the presence of basic catalysts and an aldol adduct **3a** was obtained after 30 min in 5–12% yields.

Earlier we had found that water as an additive increased the yield of solvent-free reactions under stirring. Here an addition of 1 mmol water resulted in elevation of the yield of product **3a** up to 15% (entry 5). The best yield of 22% after 30 min resulted




**1a–h** **2a**,**b** **3a–k**

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1a** | H | H | H |
| **1b** | F | H | H |
| **1c** | Br | H | H |
| **1d** | $NO_2$ | H | H |
| **1e** | Br | Br | H |
| **1f** | H | H | Et |
| **1g** | OMe | H | H |
| **1h** | Me | Me | H |

**a** $R^4$ = Me
**b** $R^4$ = H

| Reactants | Product | Yield (%) |
|---|---|---|
| **1a** + **2a** | **3a** | 98 |
| **1b** + **2a** | **3b** | 92 |
| **1c** + **2a** | **3c** | 97 |
| **1d** + **2a** | **3d** | 93 |
| **1e** + **2a** | **3e** | 91 |
| **1f** + **2a** | **3f** | 87 |
| **1g** + **2a** | **3g** | 92 |
| **1b** + **2b** | **3h** | 90 |
| **1c** + **2b** | **3i** | 96 |
| **1d** + **2b** | **3j** | 97 |
| **1h** + **2b** | **3k** | 88 |

**Scheme 1**

**Table 1** Solvent-free and on water aldol reactions of isatin **1a** with dimedone **2a**.[a]

| Entry | Solvent | Catalyst or additive | *t*/min | Yield of **3a** (%) |
|---|---|---|---|---|
| 1 | – | – | 30 | 5[b] |
| 2 | – | KF | 30 | 7[b] |
| 3 | – | NaOAc | 30 | 10[b] |
| 4 | – | NaOH | 30 | 12[b] |
| 5 | – | $H_2O$ | 30 | 15[b] |
| 6 | $H_2O$ | – | 30 | 22[b] |
| 7 | $H_2O$ | – | 60 | 39 |
| 8 | $H_2O$ | – | 120 | 75 |
| 9 | $H_2O$ | – | 180 | 98 |
| 10 | $H_2O$ | – | 240 | 96 |

[a] Sovent-free conditions: isatin **1a** (2 mmol), dimedone **2a** (2 mmol), catalyst (10 mol%) or $H_2O$ as an additive (1 mmol), grinding for 30 min; on water conditions: isatin **1a** (3 mmol), dimedone **2a** (3 mmol), stirring in water (10 ml) at ambient temperature; product **3a** was isolated by filtration. [b] NMR yield.

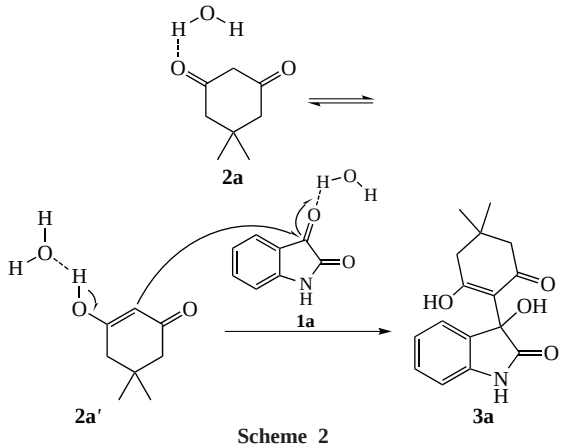
from on water conditions with stirring (entry 6). Simple increase in reaction time to 1, 2 or 3 h under the on water conditions led to formation of adduct **3a** in 39, 75 and 98% yields, respectively (entries 7–9). Under the optimal conditions thus found, namely on water reaction for 3 h with no heating or any catalyst, aldol adducts **3a**–**k** were formed in 87–98% yields (see Scheme 1).† In all these procedures the reaction mixture was finally filtered, the solid product was rinsed with chilled ethanol and dried *in vacuo*.

The structure of new compounds **3b**–**k** was confirmed by $^1$H and $^{13}$C NMR, IR spectroscopy, mass spectrometry and elemental analysis (see Online Supplementary Materials). For all the compounds only one set of signals was observed in the $^1$H and $^{13}$C NMR spectra. Compound **3a** was earlier obtaned in the electrocatalytic reaction.[21]

With all these results and taking into consideration previous data on catalyst-free aldol reaction in water,[42] a mechanism for the on water noncatalytic aldol reaction of isatin **1a** with cyclic 1,3-diketone **2a** was proposed according to Scheme 2.

In the first step, water or its clusters[43] ensure the enolization of diketone **2a** by formation of hydrogen bonds with the OH group of enol **2a′** and thus increase the nucleophilic character of methylene carbon at its 2-position. Water or its clusters simultaneously enhance electrophilic character of the carbonyl carbon of isatin **1a** through hydrogen bonds with its carbonyl oxygen.[44] Then aldol attack of enol **2a′** on the activated carbonyl group of compound **1a** takes place with the formation of adduct **3a**.

Thus, the new type of on water noncatalytic aldol reaction has been found for isatins and cyclic 1,3-diketones using catalyst-free and column chromatography-free protocol at room




**Scheme 2**

temperature with selective formation of substituted 3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-ones in high yields. This reaction represents a facile, selective and efficient way to substituted unsymmetrical scaffold containing both 3-hydroxyindolin-2-one and 3-hydroxycyclohex-3-en-1-one moieties promising for biomedical applications. The procedure is valuable from the viewpoint of environmentally benign diversity-oriented large scale processes as well as suitable for the synthesis of new potential drug libraries.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.036.

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† *General procedure for the synthesis of 3-hydroxy-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)indolin-2-ones.* Isatin **1** (3 mmol) and 1,3-cyclohexanedione **2** (3 mmol) were stirred in $H_2O$ (10 ml) at room temperature for 3 h. The solid formed was filtered off, washed with well-chilled ethanol (3 ml × 2) and dried *in vacuo* resulting in pure product **3**.

*5-Fluoro-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)indolin-2-one* **3b**. Yield 0.84 g (92%), mp 185–186 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 0.99 (s, 6H, 2Me), 1.78–2.59 (m, 2H, $CH_2$), 6.72–6.79 (m, 1H, CHAr), 6.90 (dd, 1H, $^4J_{HH}$ 1.8 Hz, $^3J_{HF}$ 7.2 Hz, CHAr), 6.97–7.04 (m, 1H, CHAr), 8.35 (br.s, 1H, OH), 10.22 (s, 1H, NH), 11.73 (br.s, 1H, OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 27.5, 27.9, 31.7, 46.0 (br.s, 2C), 78.0, 102.4, 110.0, 110.1 (d, $^3J_{CF}$ 7.2 Hz), 110.7 (d, $^2J_{CF}$ 23.1 Hz), 115.2 (d, $^2J_{CF}$ 23.1 Hz), 134.0 (d, $^3J_{CF}$ 7.2 Hz), 138.9, 157.8 (d, $^1J_{CF}$ 236.7 Hz), 176.4. MS *m*/*z* (%): 305 ($M^+$, 8), 260 (40), 244 (9), 206 (9), 165 (48), 137 (96), 109 (60), 83 (100), 56 (90), 41 (83). IR (KBr, $\nu$/cm$^{-1}$): 3148, 2963, 2718, 1737, 1629, 1590, 1488, 1370, 1248, 594. Found (%): C, 62.84; H, 5.35; N, 4.53. Calc. for $C_{16}H_{16}FNO_4$ (%): C, 62.95; H, 5.28; N, 4.59.

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