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Green Chemistry 2: A simple and Eco-friendly Synthesis in Water of 3-Substituted-3-Hydroxyindolin-2-ones.

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ABSTRACT: An efficient and environmentally benign route for the synthesis of 3-Substituted-3-hydroxyindolin-2-ones **3a-f** from an appropriate acetophenone derivatives **2a-f** and isatin **1**. Formation of **3** could be explained via aldol condensation reaction, the reaction occur at room temperature giving excellent yields and purity.
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INTRODUCTION

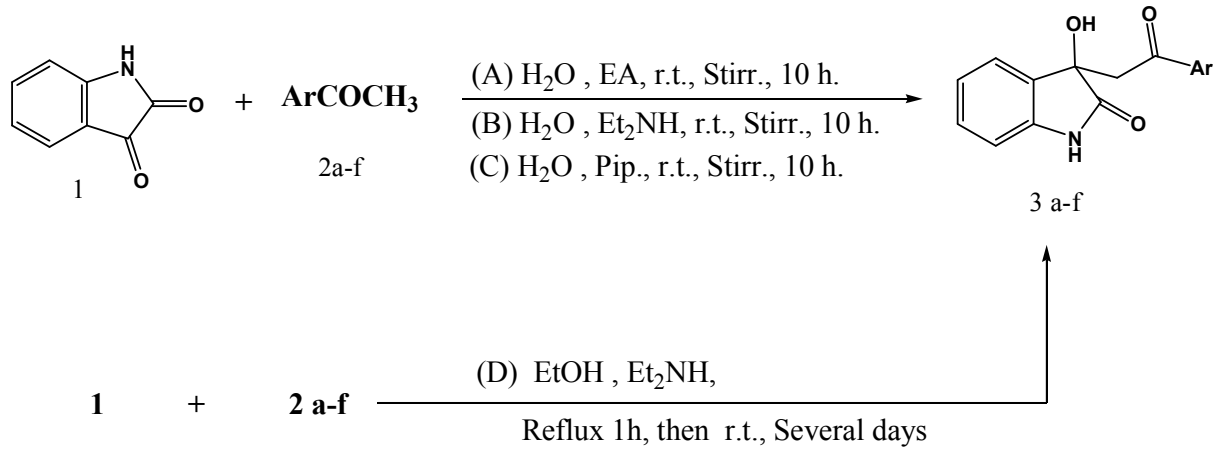
Isatins are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry. A literature survey identified several isatin derivatives in the development phase as potential new drugs. Isatin (1H-indoline-2,3-dione) is an endogenous indole found in the mammalian brain, peripheral tissues, and body fluids. It exhibits many neurophysiological and neuropharmacological effects [1]. It is a versatile compound with a diversity of effects including antibacterial [2,3], antimicrobial [4], anticonvulsant [5, 6], antiviral [7,8], anti-TB [9,10], anticancer [11,12], antimalarial [13], antioxidant [14], anti-inflammatory and analgesic activity [15,16].

3-Substituted-3-hydroxyindolin-2-ones are important substrates for studies of biological activities as well as useful synthetic intermediates for drug candidates and alkaloids. The development of practical methods for their preparation is of interest. 3-Substituted-3-hydroxyoxindoles are encountered in a large variety of natural products with a wide spectrum of biological activities, such as convolutamydines [17], donaxaridines [18], maremycins [19], dioxibrassinines [20], celogentin K [21], and 3'-hydroxy glucoisatisin [22]. 3-Alkenyl- and 3-aryl-substituted 3-hydroxyindoles [23], and their derivatives [24], have been used in a number of recent pharmaceutical studies. The formation of quaternary carbon centers via addition of nucleophiles to ketone derivatives still constitutes a major challenge for synthetic chemistry. Recently, organic reactions in water have attracted great interest in organic synthesis because of its cost, safety and environmental concern.

RESULT AND DISCUSSION

It has been reported the synthesis of 3-Substituted-3-hydroxyindolin-2-ones in refluxing ethanol and diethylamine as a catalyst for 30-60 minutes and standing in room temperature for several days[25], and by using DMF in the presence of molecular sieve (MS) 4 A^{o}, a catalyst-free aldol condensation of aromatic and aliphatic ketones with isatin under mild condition reaction[26]. There is a need to develop a generally applicable, mild, and environmentally benign practical methodology. Finally, we herein disclose a simple, benign and convenient method for the efficient synthesis of 3-Substituted-3-hydroxyindolin-2-ones in water catalyzed by ethanolamine or diethylamine or piperidine (A-C, Scheme 1).

In the present work, we have replaced the organic solvent (ethanol, DMF) by water, the most clean, simple, safe, healthy, available and environmentally benign & economic solvent (A-C, Scheme 1). Stirring **1** and the acetophenone **2a-f** in water containg catalytic amount of ethanolamine or diethylamine or piperidine, at room temperature for as short as just 10 hours reaction time afforded the planned products **3a-f** in solid forms of 78 - 98 % yields. These products **3a-f** were relatively pure.



Scheme 1

To confirm the formation and separation of **3a-f**, we have repeated the preparation of **3** by different pathways: (A-C, Scheme 1), we have followed up the reported pathway of refluxing **1** with **2a-f** in ethanol (D, Scheme 1) [25]. Melting points (m.p.), mixture melting points (mix. m.p.) thin layer chromatography (TLC) and infra red (IR) spectra have been used to confirm obtaining the same respective derivatives **3**.

EXPERIMENTAL

All melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected; IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at New Damietta, Mansoura University, Damietta branch. Microanalytical data were performed on a C, H, N Elemental Analyzer at the Faculty of Science, King Abdulaziz University, Jaddah, K.S.A.

Preparation of 3-Hydroxy-3-phenacyloxindoles (3a-f) (A-D, Scheme 1).

General Procedure

A mixture of isatin **1** (0.01 mol) , the appropriate acetophenone **2a-f** (0.01 mol) and 2 drops of ethanolamine or diethyl amine or piperidine in 40 ml distilled water was stirred at room temperature for 10h. The solid product, so formed, was collected by filtration and recrystallized from ethanol: H_2O.

3-Hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (3a).

White fine crystals: yield: 93 %; m.p:174-5 ^oC [25]; mix. m.p: 173-5 ^oC; IR (KBr, υ_{max}, cm^{-1}): 3400, 3260 (OH, NH), 3063 (CH aromatic), 2907 (CH aliphatic), 1714, 1682 (CO); **^{1}H NMR** (600 MHz, DMSO: $CDCl_3$), δ, ppm = 10.20 (1H, s, N**H**), 7.85 (2H, d, Ar-**H**), 7.55 (1H, t, Ar-**H**), 7.43 (2H, t, Ar-**H**), 7.24 (1H, d, Ar-**H**), 7.16 (1H, t, Ar-**H**), 6.88 (2H, t, Ar-**H**), 6.10 (1H, s, OH), 3.66-3.96 (2H, q, CH_2).

Anal. Calcd for $C_{16}H_{13}NO_3$ (Mol. Wt: 267.28): C, 71.90; H, 4.90; N, 5.24; Found: C, 71.83; H, 4.86; N, 5.22.

3-Hydroxy-3-(2-oxo-2-p-tolylethyl)indolin-2-one (3b).

White fine crystals: yield: 92 %; m.p: 192-3^{o}C [25]; mix. m.p: 189-192 ^{o}C; IR (KBr, υ_{max}, cm^{-1}): 3381, 3343 (OH, NH), 3061 (CH aromatic), 2896 (CH aliphatic), 1727, 1670 (CO); **^{1}H NMR** (600 MHz, DMSO: $CDCl_3$), δ, ppm = 9.65 (1H, s, N**H**), 7.78 (2H, d, Ar-**H**), 7.30 (1H, d, Ar-**H**), 7.22-7.17 (3H, m, Ar-**H**), 6.94-6.9 (2H, q, Ar-**H**), 5.69 (1H, s, OH), 3.88-3.62 (2H, dd, CH_2), 2.38 (3H, s, CH_3).

Anal. Calcd for $C_{17}H_{15}NO_3$ (Mol. Wt: 281.31): C, 72.58; H, 5.37; N, 4.98;; Found: C, 72.53; H, 5.31; N, 4.92.

3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (3c).

Yellow crystals: yield: 98 %; m.p: 198-9^{o}C [25]; mix. m.p: 197-9 ^{o}C; IR (KBr, υ_{max}, cm^{-1}): 3375, 3192 (OH, NH), 3058 (CH aromatic), 2902 (CH aliphatic), 1700, 1680 (CO); **^{13}C NMR** (150 MHz, DMSO: $CDCl_3$), δ, ppm = 195.12 (**C**O, ketone), 178.65 (**C**O, amide),

142.70, 139.12, 134.68, 131.15, 129.48, 129.08, 128.64, 123.47, 121.47, 109.82 (aromatic carbon), 73.29 (**C**-OH), 45.78 (**C**H_2).
Anal. Calcd for $C_{16}H_{12}ClNO_3$ (Cl = 35.45, Mol. Wt: 301.72): C, 63.69; H, 4.01; N, 4.64; Found: C, 63.68; H, 4.00; N, 4.62.

3-Hydroxy-3-(2-(4-hydroxyphenyl)-2-oxoethyl)indolin-2-one (3d).

Red crystals: yield: 84 %; m.p: 204-5^{o}C; IR (KBr, υ_{max}, cm^{-1}): 3418, 3232, (OH, NH), 3050 (CH aromatic), 2886 (CH aliphatic), 1727, 1618 (CO).
Anal. Calcd for $C_{16}H_{13}NO_4$ (Mol. Wt: 283.28): C, 67.84; H, 4.63; N, 4.94; Found: C, 67.79; H, 4.57; N, 4.91.

3-Hydroxy-3-(2-(2-hydroxyphenyl)-2-oxoethyl)indolin-2-one (3e).

Yellow crystals: yield: 83%; m.p: 194-6^{o}C; IR (KBr, υ_{max}, cm^{-1}): 3347, 3265, (OH, NH), 3043 (CH aromatic), 2907 (CH aliphatic), 1712, 1640 (CO); **^{1}H NMR** (600 MHz, DMSO: $CDCl_3$), δ, ppm = 10.19 (1H, s, N**H**), 7.87 (1H, d, Ar-**H**), 7.45 (1H, t, Ar-**H**), 7.28 (1H, d, Ar-**H**), 7.18 (1H, t, Ar-**H**), 6.93-6.85 (4H, m, Ar-**H**), 6.20 (1H, s, OH), 4.02-3.71 (2H, dd, CH_2).
Anal. Calcd for $C_{16}H_{13}NO_4$ (Mol. Wt: 283.28): C, 67.84; H, 4.63; N, 4.94; Found: C, 67.81; H, 4.62; N, 4.89.

3-(2-(4-aminophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (3f).

Red crystals: yield: 78%; m.p: 183-5 ^{o}C; IR (KBr, υ_{max}, cm^{-1}): 3447, 3237, (OH, NH, NH_2), 3050 (CH aromatic), 2816(CH aliphatic), 1729, 1680 (CO); **^{1}H NMR** (600 MHz, DMSO: $CDCl_3$), δ, ppm = 10.04 (1H, s, N**H**), 7.71 (2H, t, Ar-**H**), 7.63 (2H, t, Ar-**H**), 7.24 (1H, d, Ar-**H**), 7.15 (1H, t, Ar-**H**), 6.58 (2H, d, Ar-**H**), 6.00 (1H, s, NH_2), 3.77-3.49 (2H, dd, CH_2).
Anal. Calcd for $C_{16}H_{14}N_2O_3$ (Mol. Wt: 282.29): C, 68.07; H, 5.00; N, 9.92; Found: C, 68.01; H, 4.97; N, 9.88.

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