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Zinc-Mediated Entry to Functionalized 3-Substituted 3-Hydroxyindolin-2-Ones *via* a Modified Henry Reaction of Isatins with Bromonitroalkanes in Aqueous Media

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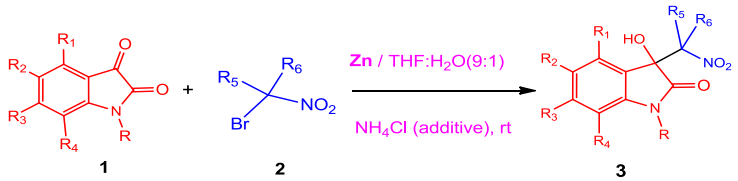
ABSTRACT

The reaction of 2,3-indolinediones (isatins) with stabilized organometallic reagents were investigated in aqueous media. The reaction between isatins and a variety of stabilized α-bromonitroalkanes undergo modified Henry reaction conditions to construct the 3-substituted 3-hydroxyindolin-2-ones in the presence of Zinc metal, THF: H_2O (9: 1) as solvent and ammonium chloride as an additive.

Keywords: Isatin, Bromonitroalkanes, Oxindoles, Zinc, Aqueous medium.

INTRODUCTION

3-Substituted 3-hydroxyoxindoles [1] are the core structural unit in a large array of fascinating natural products with a broad spectrum of intriguing biological activities, such as convolutamydines [2], dioxibrassinine [3], diazonamide, CPC-1, welwitindolinone C, spirobrassinin [4] (Figure 1), celogentin K, 3-hydroxy hydroxyglucoisatisins, and TMC-95A [1,2]. Molecules that include this structural unit constitute major targets in the development of drug candidates. 3-Alkenyl- and 3-aryl substituted 3-hydroxyoxindoles [3] and their derivatives [4] have been used in a number of recent pharmaceutical studies. Because of the excellent biological activity of these molecules, much attention has been paid for their synthesis. One of the most straightforward approaches for the synthesis of 3-substituted- 3-hydroxyindolin-2-ones is obviously a nucleophilic addition of appropriate nucleophiles to isatins. Recently, several elegant approaches for the synthesis of such compounds have been reported using metal-based catalysts [5-8]. One of the reported method accomplished the synthesis of 3-hydroxy-3-(nitromethyl)indolin-2-ones by using base in organic solvents (Scheme). Other methods includes the Henry reaction of isatin induced by an electrochemical method [9] which require special instrumental setup or a quinidine (QD)/cinchona alkaloid catalyzed reaction of isatin [10]. However, these methods suffer from certain drawbacks such as tedious work-up, longer reaction time, unsatisfactory yields and narrow scope of substrates.



R = H, C_3H_5, Ph, Bn R_5 , R_6 = H, Me

R_1 = R_2= R_3= R_4= H, 5-CH_3, 5-F, 5-Cl, 5-Br, 5-I , 5-NO_2, 5-OCF_3, 4-Br,7-Cl, 7-Br, 4,6-di Bromo, 5,7-di Bromo.

Scheme

In recent years, the applications of metal-promoted reactions in organic synthesis have become a new research focus [11]. Particularly, Zinc mediated reactions have gained broad popularity in organic synthesis. Zn-Metal has been used in organic reactions like Reformatsky reaction [12], Pinacol coupling [13] and Clemmensen reduction [14]. The main advantages of zinc mediated reactions are efficiency, reusability, simple workup procedure and easy to isolation of the products.

To the best of our knowledge there is no report on the reaction of isatin with bromonitroalkane to construct the 3-substituted 3-hydroxyindolin-2-ones. As a part of our ongoing research in the development of new methodologies for the synthesis of 3-Hydroxy disubstituted oxindole [15-19]. In this paper, we disclose that the Zn-mediated Henry reaction of readily accessible bromonitroalkanes with isatins in presence of Zn in aq. THF.

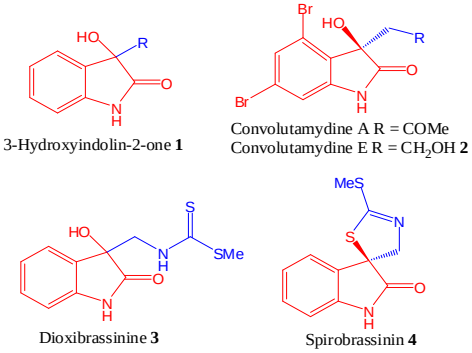


Figure 1: Natural products containing the 3-hydroxy indolin-2-one structural framework.

Our optimization studies began with the exploration of various metals like Sn, In, Zn and different solvent ratios for the Henry reaction of bromonitromethane with isatin (Table 1). After screening of these metals, it was observed that the reaction proceeded efficiently using Zn (Table 1, entry 10) and resulted in high yields of the desired product after short reaction time (1-5 h). However, with other metals the yield of the desired product invariable even if the reaction was prolonged to 24 h. We have attempted different solvent ratios of THF/H_2O (9: 1, 9.5: 0.5, 1: 1). During the experiments we observed the reactivity profile of metals is as follows Zn>In>Sn. Finally, we found that the THF/H_2O (9: 1) was suitable for the optimum conversion.

Table 1: Screened metals for the reaction of Isatin with Bromonitromethane/nitroethane

Entry	Metal	Solvent	Time (h)	Yield (%)
1	Sn	H_2O	8	Trace
2	Sn	THF	5	35
3	Sn	THF/H_2O (1: 1)	10	55
4	Sn	THF/H_2O (9: 1)	7	65
5	In	THF	6	46
6	In	H_2O	8	42
7	In	THF/H_2O (9: 1)	4	70
8	Zn	H_2O	10	50
9	Zn	THF	8	40
10	Zn	THF/H_2O (9: 1)	3	90
11	Zn	THF/H_2O (9.5: 0.5)	4.5	75
12	Zn	THF/H_2O (1: 1)	6	65

With the optimized conditions in hand, a variety of isatins were next explored to investigate the generality of this reaction and the detailed results are summarized in Table 2. The addition of bromonitromethane 2a to various isatins 1 proceeded readily and resulted into expected product. Though, the reaction proceeded with 1:1 ratio of reactant, the best results were obtained by using two equivalents of bromonitromethane. Further, we have extended this protocol to different substituted isatins, for example, 5-halo isatins reacted with bromonitromethane 2a under the standard reaction conditions and resulted into high yields (Table 2, entries 6-9). Other 5-substituted isatins were converted into desired products in good yields (Table 2, entries 10-12). The Henry reaction is also applicable to N-substituted isatins (Table 2, entry 2-5) the corresponding products were obtained in good yields. Similarly, 4-substitued, 7-substitued and also disubstitued isatins (Table 2, entries 13-17) participated in the reaction and lead to the products in lower yields.

Reaction conditions

Isatin (1 equiv.), Bromonitro methane/ethane (2 equiv.), Zn (2 equiv.), NH_4Cl (additive) in THF: H_2O (9: 1) at 20ºC, isolated yields.

Table 2: 3-hydroxy-3-(nitromethyl) indolin-2-one derivatives formation by using Zn/THF: H_2O (9: 1).

Entry	R	R1	R2	R3	R4	R5	R6	Time (min)	Yields (%)[a]
1	H	H	H	H	H	H	H	3	95
2	Me	H	H	H	H	H	H	3.5	90
3	Bn	H	H	H	H	H	H	3	88
4	Bn	H	Br	H	H	H	H	3	90
5	Ph	H	H	H	H	H	H	2.5	82
6	H	H	F	H	H	H	H	3	93
7	H	H	Cl	H	H	H	H	3.5	90
8	H	H	Br	H	H	H	H	3	89
9	H	H	I	H	H	H	H	1.5	93

10	H	H	NO_2	H	H	H	H	5	85
11	H	H	OCF_3	H	H	H	H	4.5	86
12	H	Br	H	H	H	H	H	5	70
13	H	Br	H	Br	H	H	H	5	75
14	H	H	Br	H	Br	H	H	4.5	77
15	H	H	H	H	Br	H	H	5	72
16	H	H	H	H	Cl	H	H	5	70
17	H	Cl	H	H	Cl	CH_3	H	3	71
18	H	H	Br	H	H	CH_3	H	4	91 (70: 30)[b]
19	H	H	I	H	H	CH_3	H	2	94 (80: 20)[b]
20	H	H	H	H	H	CH_3	H	2	90 (60: 40)[b]
21	H	H	H	H	H	CH_3	CH_3	2	86
22	H	H	F	H	H	CH_3	CH_3	2	75
23	H	H	Br	H	H	CH_3	CH_3	2	77
24	Ph	H	H	H	H	CH_3	C_H3	2	72
25	Bn	H	H	H	H	CH_3	CH_3	2	70

b: Diastereomeric ratio

When the reaction was examined with bromonitroethane 2b which gave good yields and the Henry products were obtained as a mixture of diastereomers (Table 2, entry 18-20). Analogously, the reaction of 2-bromo-2-nitropropane 2c with isatins proceeded smoothly to furnish the expected product is good yield (Table 2, entries 21-25). Though this method requires the additional step to prepare the bromonitroalkane this was greatly compensated by a broad substrate scope and efficiency of reaction.

MATERIALS AND METHODS

General procedure for the synthesis of 3-Substituted 3-hydroxyoxindoles

To a solution of bromonitroalkane 2 (2 mmol) in a mixture of solvent (THF: H_2O: 9: 1, 10 ml), Zn powder (2 mmol) and NH_4Cl (1 mol %) was added and mixture stirred for 5 minutes. Then isatins 1 (1 mmol) were added and stirred for stipulated time (See table 2). The reaction is monitored by TLC. After completion of reaction, the mixture was extracted with ethyl acetate (3 × 5 ml). The combined organic layer washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure (rotary evaporator). The crude products were purified by silica gel column chromatography using ethylacetate/hexanes (3: 7). All compounds were characterised by (M. P., NMR, Mass and IR) spectral data.

Spectral data for selected compounds

3-Hydroxy-3-(nitromethyl)indolin-2-one (Table 2, Entry-1)

White solid; M. P. 139 ºC-141ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.81 (*d*, *J*=12.6, 1H), 4.88 (d, *J*=12.6 Hz, 1H), 6.50 (s, 1H), 6.85 (d, *J*=7.3 Hz, 1H), 6.95 (t, *J*=7.3 Hz, 1H), 7.21 (t, *J*=7.3 Hz, 1H), 7.31 (d, *J*=7.3 Hz, 1H), 10.30 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=78.2, 95.4, 109.8, 121.5, 124.3, 127.6, 129.8, 142.4, 175.6; IR (KBr) ν=3263, 1734, 1621, 1550, 1468, 1186, 1103, 754 cm^{-1}; MS (ESI): *m/z* 231 (M^+ Na).

3-Hydroxy-5-methyl-3-(nitromethyl)indolin-2-one (Table 2, Entry-2)

White solid; M. P. 140ºC-142ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d6): δ (ppm)=2.30 (s, 3H), 4.72-4.83 (m, 2H), 6.43 (s, 1H), 6.70 (d, *J*=7.9 Hz, 1H), 6.98 (d, *J*=7.9 Hz, 1H), 7.09 (s, 1H), 10.20 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=20.5, 72.8, 109.7, 125.1, 124.3, 127.9, 130.8, 138.7, 140.0, 175.0; IR (KBr) ν=3172, 29244, 1737, 1625, 1553, 1498, 1304, 1027, 825 cm^{-1}; MS (ESI): *m/z* 245 (M^+ Na).

1-Benzyl-3-hydroxy-3-(nitromethyl)indolin-2-one (Table 2, Entry-3)

Pale yellow solid; M. P. 125ºC-127ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.82-4.92 83 (m, 2H), 4.95-5.06 (m, 2H), 6.71 (d, *J*=7.7 Hz, 1H), 6.80 (s, 1H), 7.02 (t, *J*=7.5 Hz, 1H), 7.23-7.32 (m, 6H), 7.42 (d, *J*=7.2, 1H); ^{13}C-NMR (70 MHz, $CDCl_3$+DMSO-d6): δ (ppm)=41.7, 72.4, 78.2, 109.5, 116.9, 122.4, 124.3, 127.2, 130.2, 131.4, 143.0, 174.0; IR (KBr) ν=3417, 2927, 1737, 1621, 1551, 1469, 1178, 1030, 754 cm^{-1}; MS (ESI): *m/z* 299 (M^+Na).

1-Benzyl-5-bromo-3-hydroxy-3-(nitromethyl)indolin-2-one (Table 2, Entry-4)

Pale yellow solid; M. P. 121ºC-123ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.85 (d, *J*=15.8 Hz, 1H), 4.95 (d, *J*=15.8 Hz, 1H), 5.05 (s, 2H), 6.66 (d, *J*=8.3 Hz, 1H), 6.95 (s, 1H), 7.41-7.19 (m, 6H), 7.62 (s, 1H); ^{13}C-NMR (70 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=48.7, 77.7, 83.0, 101.0, 116.6, 120.0, 132.4, 132.7, 134.7, 135, 138.1, 140.4, 147.6, 179.2; IR (KBr) ν=3331, 2921, 1711, 1621, 1561, 1391, 1097, 757 cm^{-1}; MS (ESI): *m/z* 399 (M^+ Na).

3-Hydroxy-3-(nitromethyl)-1-phenylindolin-2-one (Table 2, Entry-5)

White solid; M. P. 99ºC-101ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.92-5.11 (m, 2H), 6.75 (d, *J*=7.7 Hz, 1H), 6.91 (s, 1H), 7.08 (t, *J*=7.4 Hz, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 7.40-7.55 *(*m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=72.7, 78.4, 109.1, 122.3, 125.4, 126.4, 128.1, 128.4, 129.7, 133.8, 140.2, 143.7, 174.1; IR (KBr) ν=3328, 2933, 1709, 1617, 1559, 1467, 1389, 761 cm^{-1}; MS (ESI): *m/z* 307 (M^+Na).

5-fluoro-3-hydroxy-3-(nitromethyl)indolin-2-one (Table 2, Entry-6)

White solid; M. p. 161ºC-163ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.90-4.82 (m, 2H), 6.69 (s, 1H), 6.84-6.80 (m, 1H), 6.94 (dt, *J*=2.2, 9.0 Hz, 1H), 7.14 (d, *J*=7.7 Hz, 1H), 10.39 (s, 1H); ^{13}C-NMR(75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=72.9, 78.0, 110.8, 112.7, 116.6, 129.7, 138.7, 159.4, 175.8; IR (KBr) ν=3358, 3271, 2924, 1726, 1612, 1555, 1470, 1374, 1182, 744 cm^{-1}; MS (ESI): *m/z* 249 (M^+Na).

5-Chloro-3-hydroxy-3-(nitromethyl)indolin-2-one (Table 2, Entry-7)

White solid; M. P. 253ºC-255ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.89 (*s*, 2H), 6.74 (*s*, 1H), 6.85 (*d*, *J*=8.0, 1H), 7.23 (*d*, *J*=8.0 Hz, 1H), 7.38 (*s*, 1H), 10.54 (s, 1H); ^{13}C-NMR(75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=72.6, 77.8, 111.4, 124.0, 124.8, 125.7, 129.9, 141.4, 175.5; IR (KBr) ν=3346, 3271, 2924, 1713, 1617, 1558, 1479, 1188, 1087, 833 cm^{-1}; MS (ESI): *m/z* 264 (M^+Na).

5-Bromo-3-hydroxy-3-(nitromethyl)indol-2-one (Table 2, Entry-8)

White solid; M. P. 167ºC-169ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.87 (d, *J*=2.6, 2H), 6.68 (s, 1H), 6.81 (d, *J*=8.3, 1H), 7.36 (dd, *J*=1.8, 8.1 Hz, 1H), 7.49 (d, *J*=1.8, 1H), 10.48 (s, 1H); ^{13}C-NMR(75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=72.5, 77.8, 111.9, 113.3, 127.5, 130.4, 132.7, 141.8, 175.4; IR (KBr) ν=3394, 3273, 2927, 1733, 1616, 1548, 1477, 1183, 1088, 827 cm^{-1}; MS (ESI): *m/z* 308 (M^+Na).

3-Hydroxy-5-iodo-3-(nitromethyl) indolin-2-one (Table 2, Entry-9)

White solid; M. P. 274ºC-276ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.91-4.81 (m, 2H), 6.66 (s, 1H), 6.70 (d, *J*=8.3 Hz, 1H), 7.53 (dd, *J*=1.7, 8.3 Hz, 1H), 7.64 (d, *J*=1.5 Hz, 1H), 10.46 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm)=72.6, 78.1, 84.2, 112.6, 130.5, 133.1, 138.6, 142.4, 175.2; IR (KBr) ν=3388, 3271, 2924, 1726, 1612, 1555, 1471, 1182, 822 cm-1; MS (ESI): *m/z* 357 (M^+Na).

3-Hydroxy-5-nitro-3-(nitromethyl)indol-2-one (Table 2, Entry-10)

White solid; M. P. 145ºC-147ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.90 (d, *J*=13.5, 1H), 5.06 (d, *J*=13.5, 1H), 6.85 (s, 1H), 7.00 (d, *J*=9.0, 1H), 8.18 (dd, *J*=2.2, 7.9 Hz, 1H), 8.30 (d, *J*=2.2, 1H), 11.0 (s, 1H); ^{13}C-NMR(75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=72.0, 77.3, 110.92, 120.6, 127.5, 129.1, 142.2, 149.0, 176.2; IR (KBr) ν=3324, 3273, 2927, 1743, 1696, 1558, 1534, 1487, 1188, 1089, 847 cm-1; MS (ESI): *m/z* 276 (M^+Na).

3-Hydroxy-3 (nitromethyl)-5-(trifluoromethoxy)indolin-2-one (Table 2, Entry-11)

Pale yellow solid; M. P. 115ºC-117ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.88 (s, 2H), 6.76 (s, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 7.10 (d, *J*=8.4 Hz, 1H), 7.30 (s, 1H), 10.55 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=84.6, 91.4, 111.5, 113.4, 113.9, 121.7, 128.9, 134.7, 156.5, 179.6; IR (KBr) ν=3258, 3171, 2944, 1722, 1632, 1545, 1374, 1102, 748 cm^{-1}; MS (ESI): *m/z* 315 (M^+Na).

1-Allyl-3-hydroxy-3-(nitromethyl)indolin-2-one (Table 2, Entry-12)

White solid; M. p. 171ºC-163ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.28-4.34 (m, 2H), 5.02 (m, 2H), 5.20-5.29 (m, 2H), 5.78-5.87 (m, 1H), 6.83 (*s*, 1H), 6.92 (d, *J*=7.7, 1H), 7.06 (t, *J*=7.5 Hz, 1H), 7.31 (t, *J*=7.7, 1H), 7.46, (d, *J*=7.1, 1H); ^{13}C-NMR(75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=41.5, 72.4, 78.2, 109.2, 116.9, 122.4, 124.3, 127.2, 130.2, 131.4, 143.0, 174.0; IR (KBr) ν=3374, 2925, 1731, 1614, 1554, 1469, 1373, 1186, 1072, 755 cm-1; MS (ESI): *m/z* 249 (M^+1).

3-Hydroxy-4,6-dibromo-3-(nitromethyl)indolin-2-one (Table 2, Entry-13)

White solid; Mp 195ºC-197ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.95 (d, *J*=13.4 Hz, 1H), 5.30 (d, *J*=13.4 Hz, 1H), 6.75 (s, 1H), 6.98 (s, 1H), 7.23 (s, 1H), 10.75 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=83.4, 87.7, 113.5, 122.0, 124.5, 126.6, 129.4, 144.2, 179.6; IR (KBr) ν=3356, 3178, 1714, 1610, 1556, 1373, 1064, 846 cm^{-1}; MS (ESI): *m/z* 387 (M^+H).

3-Hydroxy-5,7-dibromo-3-(nitromethyl)indlin-2-one (Table 2, Entry-14)

White solid; M. P. 163ºC-165ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.90 (s, 2H), 6.83 (s, 1H), 7.47 (d, *J*=1.5 Hz, 1H), 7.53 (d, *J*=1.51 Hz, 1H), 10.75 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=84.4, 89.7, 105.5, 118.4, 127.5, 132.3, 133.4, 140.0, 179.6; IR (KBr) ν=3346, 3148, 1718, 1625, 1566, 1014, 856 cm^{-1}; MS (ESI): *m/z* 387 (M^+ H), (M^+ 2).

3-Hydroxy-7-bromo-3-(nitromethyl)indolinin-2-one (Table 2, Entry-15)

White solid; M. P. 136ºC-138ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.90 (d, *J* = 6.2 Hz, 2H), 6.76 (s, 1H), 6.90 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J*=11.3 Hz, 1H), 7.38 (d, *J*=11.8 Hz, 1H), 10.64 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=73.3, 78.4, 102.4, 123.0, 123.1, 129.2, 132.7, 141.7, 175.4; IR (KBr) ν=3196, 1717, 1612, 1550, 1443, 777 cm^{-1}. MS (ESI): *m/z* 308 (M^+ Na).

7-Chloro-3-hydroxy-3-(nitromethyl)indolin-2-one (Table 2, Entry-16)

White solid; M. P. 136ºC-138ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=4.80(q, 2H), 6.71 (s, 1H), 6.92 (d, *J* = 8.0, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J*=7.0, 1H), 10.60 (s, 1H); ^{13}C-NMR(75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=73.2, 78.1, 114.2, 123.3, 126.4, 129.9, 130.2, 140.3, 175.9; IR (KBr) ν=3346, 1713, 1617, 1558, 1471, 1188, 1087, 833 cm^{-1}; MS (ESI): *m/z* 264 (M^+Na).

4,7-Dichloro-2-methylene-3-(nitromethyl)indolin-2-one (Table 2, Entry-17)

White Solid; Mp 152ºC-154ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm)=5.08 (d, *J*=13.2 Hz, 2H), 6.88 (s, 1H), 6.91 (d, *J*=8.4 Hz, 1H), 7.21 (d, *J*=8.4 Hz, 1H), 10.74 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm)=84.0, 85.6, 125.4, 126.2, 128.8, 129.2, 132.8, 144.8, 179; IR (KBr) ν=3551, 3248, 2974, 1727, 1619, 1552, 1488, 1078, 512 cm^{-1}; MS (ESI): *m/z* = 299 (M^+ Na).

5-Bromo-3-hydroxy-3-(1-nitroethyl)indolin-2-one (Table 2, Entry-18)

White solid; M. P. 167ºC-169ºC; diastereomeric ratio 70:30; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=1.40 (d, *J*=6.9 Hz, 3H), 5.0 (q, 1H), 6.73 (s, 1H), 6.77-6.81 (m, 1H), 7.34-7.40 (m, 1H), 7.51 (s, 1H), 10.50 (s, 1H) (Major); 1.77 (d, *J*=6.9 Hz, 3H), 4.98 (*q*, 1H), 6.68 (s, 1H), 6.83-6.87 (m, 1H), 7.20-7.30 (m, 1H), 7.34 (s, 1H), 10.43 (s, 1H) (Minor); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=6.8, 89.6, 96.9, 118.8, 123.8, 129.4, 133.0, 133.2, 139.6, 179.2 (Major); 6.4, 88.9, 96.2, 118.2, 124.0, 128.8, 129.6, 133.4, 139.2, 178.8 (Minor); IR (KBr) ν=3356, 1729, 1628, 1572, 1558, 1487, 1371, 1161, 847 cm^{-1}; MS (ESI): *m/z* 323 (M^+Na).

5-Iodo-3-hydroxy-3-(1-nitroethyl)indolin-2-one (Table 2, Entry-19)

White solid; M. P. 278ºC-280ºC; diastereomeric ratio 80: 20; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=1.40 (d, *J*=6.9 Hz, 3H), 4.50 (s, 1H) 4.96 (q, 1H), 6.70 (d, *J*=8.2 Hz, 1H), 7.55-7.60 (m, 1H), 7.68 (s, 1H), 10.451 (s, 1H) (Major); 1.77 (d, *J*=6.9 Hz, 3H), 4.52 (s, 1H), 5.02 (q,

1H), 6.75 (d, *J* = 8.1 Hz, 1H), 7.57-7.62 (m, 2H), 10.38 (s, 1H) (Minor); ^{13}C-NMR (75 MHz, $CDCl_3$ +DMSO-d_6): δ (ppm)=6.78, 89.6, 97.4, 110.7, 113.0, 115.4, 132.4, 136.5, 158.6, 179.4 (Major); 6.74, 89.4, 97.3, 110.2, 113.4, 115.0, 132.0, 136.7, 158.2, 179.4 (Minor); IR (KBr) ν = 3381, 3248, 2934, 1733, 1614, 1552, 1472, 1188, 816 cm^{-1}; MS (ESI): *m*/*z* 371 (M^+Na).

3-Hydroxy-3-(1-nitroethyl)indolin-2-one (Table 2, Entry-20)

Pale yellow solid; M. P. 110ºC-112ºC; diastereomeric ratio 60:40; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)= 1.35 (d, *J* = 6.7 Hz, 3H), 4.0 (*s*, 1H), 4.95 (q, 1H), 6.80-7.10 (m, 3H), 7.18 (dd, *J* = 2.4, 5.8 Hz, 1H), 10.46 (*s*, 1H) (Major); 1.74 (*d*, *J* = 6.7 Hz, 3H), 3.9 (s, 1H), 5.43 (q, 1H), 6.90-7.05 (m, 3H), 7.30-7.40 (*m*, 1H), 10.36 (*s*, 1H) (Minor); ^{13}C-NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm)=7.2, 88.6, 98.4, 110.2, 123.6, 124.4, 126.8, 131.2, 141.0, 176.0 (Major); 6.9, 89.2, 97.3, 109.0, 122.4, 123.8, 125.6, 131.0, 140.8, 176.4 (Minor); IR (KBr) ν = 3250, 2906, 1717, 1630, 1552, 1480, 1313, 1088 cm^{-1}; MS (ESI): *m*/*z* 245 (M^+Na).

2-Methylene-3-(2-nitropropan-2-yl)indolin-2-one (Table 2, Entry-21)

White solid; M. P. 164ºC-166ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm)=1.25 (s, 6H), 4.93 (s, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 7.0 (t, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.50-7.55 (m, 1H), 9.83 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm)=15.8, 92.8, 104.0, 107.8, 123.0, 124.0, 125.7, 133.9, 141.0, 179.6; IR (KBr): ν = 3250, 2906, 1717, 1630, 1552, 1480, 1313, 1088 cm^{-1}; MS (ESI): *m*/*z* 259 (M^+Na), 290 (M^+1).

5-Fluoro-2-methylene-3-(2-nitropropan-2-yl)indolin-2-one (Table 2, Entry-22)

Yellow solid; M. P. 96ºC-98ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm)=2.03 (*s*, 6H), 6.09 (s, 1H), 6.85-6.90 (m, 1H), 7.03-7.09 (m, 1H), 7.68 (d, *J* =7.7 Hz, 1H) 10.0 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm)=15.4, 91.8, 97.7, 123.9, 124.8, 127.6, 132.3, 133.8, 144.3, 179.5; IR (KBr): ν=3560, 1618, 1476, 1378, 1274, 1158, 1128, 945, 769 cm^{-1}. MS (ESI): *m*/*z* 277 (M^+Na).

5-Bromo-2-methylene-3-(2-nitropropan-2-yl)indolin-2-one(Table 2, Entry-23)

Paleyellow solid; Mp 135ºC-137ºC; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm)= 2.04 (s, 6H), 6.89 (s, 1H), 7.53-7.65 (m, 3H), 10.05 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm)=15.0, 93.0, 104.6, 116.7, 122.8, 128.0, 132.9, 135.0, 140.3, 179.1; IR (KBr): 3558, 161, 1396, 1133, 821, 678, 510 cm-1; MS (ESI): *m*/*z* 337 (M^+Na).

3-Hydroxy-3-(2-nitropropan-2-yl)-1-phenylindolin-2-one (Table 2, Entry-24)

White solid; Mp 117ºC-119ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=1.63 (s, 6H), 6.71 (d, *J*=7.7 Hz, 1H), 6.93 (*s*, 1H), 7.10 (t, *J*=7.4 Hz, 1H), 7.24 (t, *J*=7.5 Hz, 1H), 7.40-7.55 (*m*, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ (ppm)=15.0, 93.1, 102.0, 116.1, 117.4, 121.2, 124.6, 126.8, 126.6, 129.6, 130.1, 140.3, 143.5, 175.6; IR (KBr) ν=3528, 2933, 1709, 1617, 1559, 1467, 1389, 761 cm^{-1}; MS (ESI): *m*/*z*=335 (M^+ Na).

1-Benzyl-3-hydroxy-3-(2-nitropropan-2-yl)indolin-2-one (Table 2, Entry-25)

White solid; M. P. 112ºC-114ºC; ^{1}H-NMR (300 MHz, $CDCl_3$+DMSO-d_6): 1.60 (s, 6H), 4.83 (d, *J*=15.4 Hz, 1H), 4.96 (d, *J*=15.4 Hz, 1H), 5.08 (s, 1H), 6.43 (d, *J*=8.3 Hz, 1H), 6.95 (s, 1H), 7.39-7.19 (*m*, 6H), 7.58 (*s*, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm)=15.3, 50.6, 82.8, 101.6, 114.0, 123.4, 123.8, 125.9, 126.9, 128.5, 132.8, 136.1, 144.2, 179.0; IR (KBr): 3558, 1619, 1396, 1133, 821, 678, 510: MS (ESI): *m*/*z* 349 (M^+ Na).

CONCLUSION

In conclusion, we have demonstrated a metal mediated an efficient method for the synthesis of functionalized 3-hydroxy-3-(nitromethyl)indolin-2-one derivatives in aqueous media. The present method provides a general protocol for the synthesis of variety of substituted and functionalized oxindoles of biologically interest.

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REFERENCES

[1] S. Peddibhotla, *Curr. Bioact. Compd*., **2009**, 5, 20.
[2] Y. Kamano, H.P. Zhang, Y. Ichihara, H. Kizu, K. Komiyama, G. R. Pettit, *Tetrahedron Lett.*, **1995**, 36, 2783.
[3] P. Hewawasam, A.N. Meanwell, V. K. Gribkoff, S.I. Dworetzky, C.G. Biossard, *Bioorg. Med. Chem. Lett*., **1997**, 7, 1255.
[4] P. Hewawasam, N.A. Meanwell, V.K. Gribkoff, U.S. Patent 5, **1997**, 602, 169.
[5] R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem. Int. Ed*., **2006**, 45, 3353.
[6] Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc*., **2005**, 127, 10164.
[7] S. Lee, J.F. Hartwig, *J. Org. Chem*., **2001**, 66, 3402.
[8] V. Schulz, M. Davoust, M. Lemarie, J.F. Lohier, J. Sopkova de Oliveira Santos, P. Metzner, J.F. Briere, *Org. Lett*., **2007**, 9, 1745.
[9] W.R. Conn, H.G. Lindwall, *J. Am. Chem. Soc.*, **1936**, 58, 1236.
[10] Lu Liu, Z. Shilei, X. Fei, G. Lou, Z. Haoyi, S. Ma, D. Wenhu, W. Wei, *Chem. Eur. J.*, **2011**, *17*, 7791.
[11] H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.*, **2007**, 129, 5376.
[12] E. Oler, K. Reininger, U. Schmidt, *Angew. Chem. Int.Ed.*, **1970**, 9, 457.
[13] Z. Hui, D. Wei, Qing Xaing, *Chine. Chem. Lett.*, **2005**, 16, 1459.
[14] Y. Shosuke, T. Masaaki, H. Yoshimsa, *Org. Synth.*, **1988,** 6, 289.
[15] A.S. Kumar, G.S. Kumar, K. Ramakrishna, P. Ramesh, A. Swetha, H.M. Meshram, *Synlett.*, **2017**, 28, 337.
[16] K. Ramakrishna, K.A. Sanjeeva, K.G. Santosh, H.M. Meshram, *Chemistry Select.*, **2017**, 2, 5105-5109.
[17] A.S. Kumar, P. Ramesh, G.S. Kumar, A. Swetha, J.B. Nanubolu, H.M. Meshram, *RSC. Adv.*, **2016**, 6, 1705.
[18] A.S. Kumar, P. Ramesh, G.S. Kumar, J.B. Nanubolu, T.P. Rao, H.N. Meshram, *RSC. Adv.*, **2015**, 5, 51581.
[19] H.M. Meshram, P. Ramesh, A.S. Kumar, A. Swetha, *Tetrahedron Lett.*, **2011**, 52, 5862.