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Cp_2ZrCl_2-induced Reformatsky and Barbier reactions on isatins: an efficient synthesis of 3-substituted-3-hydroxyindolin-2-ones

Mangilal Chouhan, Ratnesh Sharma and Vipin A. Nair*

A mild and rapid one-pot process for Reformatsky and Barbier reactions using a catalytic quantity of zirconocene dichloride (Cp_2ZrCl_2) as a promoter and zinc as a terminal reductant at room temperature in dimethyl formamide was developed. The protocol has wide substrate suitability and afforded the desired 3-substituted-3-hydroxyindolin-2-ones from istains in good yields and short reaction time. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: zirconocene dichloride; zinc; α-bromoethylester; benzylbromide; isatin

Introduction

3-Substituted-3-hydroxyindolin-2-ones have gained much attention because of their key structural resemblance to several drug candidates and natural products, such as convolutamydines, diazonamide A, leptosin D, 3′-hydroxyglucoisatisin, witindolinone C, TMC-95s, celogentin K and dioxibrassinine as well as several other biologically active compounds (Fig. 1).[1–6] 3-Substituted-3-hydroxyindolin-2-ones are known to possess antibacterial, antiprotozoal and anti-inflammatory activities and have also demonstrated agonistic activity with progesterone receptors, the activities being influenced by the substituent at the C-3 position as well as the absolute configuration at the stereogenic center.[7–9]

Among the reports available[10–13] on the synthesis of 3-hydroxyindolin-2-ones from isatin derivatives, synthetic procedures involving Baylis–Hillman reaction[10] or oxidation of 3-alkylindoles by $CeCl_3{}^{\bullet}7H_2O$/IBX[13] (Scheme 1) have demonstrated wider scope and applicability. Although unique, these methods are considerably time-consuming and/or expensive, making it important to develop a highly efficient method for their synthesis; this defines our interest. One of the most straightforward approaches would be a carbon–carbon bond-forming reaction in which a nucleophile adds to isatin in the presence of either a metal-based catalyst[14–17] or an organocatalyst.[18] The Reformatsky reaction[19] is a well-known method in which a metal, usually zinc, is inserted between the carbon–halogen bond of an α-halo carbonyl compound under neutral conditions. It offers regioselective enolate formation and upon reaction with carbonyl compounds yield β-hydroxyesters. The nucleophilic character coupled with low basicity makes the Reformatsky reaction a better alternative in total synthesis where selectivity poses problems, but the classical method suffers from limitations such as pre-activation of the metal, high reaction temperature, longer reaction time and formation of undesired Claisen and homocoupled products.[20,21] To overcome such issues, several approaches have been developed such as the use of other metals,[22–28] low-valent organometallic species[29–32] and *in situ* activation of metal by a sonochemical path.[33] Zirconium is known to play a significant role in various synthetic transformations.[34–37] In continuation of our work on zirconium-mediated reactions,[38,39] we have examined the feasibility of this transition metal for the synthesis of 3-hydroxyindolin-2-ones.

Results and Discussion

For a detailed investigation, the Reformatsky reaction of ethyl bromoacetate with 4-chlorobenzaldehyde was carried out. The reaction mediated by zinc was tested in the presence of various zirconium catalysts, viz. $ZrOCl_2$, $ZrCl_4$, Cp_2ZrCl_2 and $CpZrCl_3$ (Table 1). We observed that Cp_2ZrCl_2 provided the maximum yields of the product, in a short time of 5 min, at an optimum catalytic concentration of 10 mol%. The reaction was further attempted with different metal reductants such as Fe, Mg, Sn, Mn and Zn (Table 2). Poor yields and long reactions times decreased the usefulness in the first three cases. A drastic improvement was observed with Mn while Zn was found to be superior. Among the various solvents tried, the polar aprotic solvent dimethyl formamide (DMF) turned out to be the best (Table 3). The thermal dependency of the reaction was analyzed at three different temperatures of 0, 25 and 50 °C. At 0 °C, the reaction was sluggish affording only trace amounts of the desired product along with the starting material. Although the starting material was completely consumed at 50 °C, the formation of only side products could be observed. Maximum yield was obtained at 25 °C in 5 min. From the above observations we inferred that reacting 0.1 equiv. of Cp_2ZrCl_2, 2.0 equiv. of zinc and 1.5 equiv. of α-bromoester with 1.0 equiv. of the carbonyl compound in DMF as the solvent at 25 °C would be the ideal conditions for the reaction. The scope of the optimized condition was tested on various aldehydes and ketones (Scheme 2), which afforded β-hydroxyesters in good yields (Table 4). Reactions with α-methyl α-bromoester afforded

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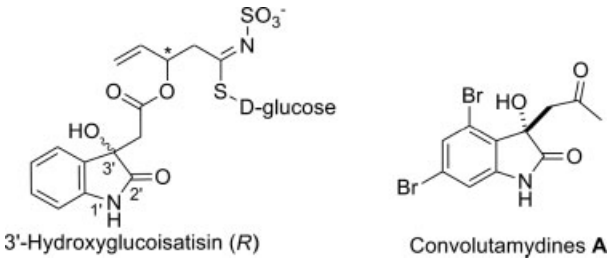


Figure 1. Biologically active natural products with 3-substituted-3-hydroxyindolin-2-ones as core unit.

diastereomers favoring the thermodynamically more stable *anti* isomer (entries 6–8 and 13–16, Table 4).

Encouraged by the results obtained, our efforts were then directed to obtain 3-substituted-3-hydroxyindolin-2-ones from isatins (Scheme 3), employing this one-pot process. The reactions were highly successful with satisfactory yields of the desired products (entries 1–6, Table 5). The reaction tolerated both electron-withdrawing and electron-donating groups alike. However, no diastereoselectivity could be observed in the reactions when carried out with α-methyl α-bromoesters. The reaction condition was further extended to the Barbier reaction on isatins with benzyl halides to yield 3-benzyl-3-hydroxyindolin-2-one derivatives (entries 7–15, Table 5). Based on this successful strategy, a plausible mechanism was depicted, as illustrated in Fig. 2. It is well known that, for all metal-mediated additions of organic halides, the necessary condition is the ability of a metal in its active form to insert into the carbon–halogen bond to generate an organometallic species which can be trapped with various electrophiles.[27,28] The Lewis acid Cp_2ZrCl_2 is expected to influence the course of the reaction through dual activation. It can activate the organic halide by coordination and increase the feasibility of insertion of zinc between the carbon–halogen bond.[40] The activated organic halide is thus easily reduced to the organozinc intermediate (**A**), facilitating the reactions with isatins to afford the desired products. Additionally, the electrophilicity of isatins may also be enhanced by Cp_2ZrCl_2, which makes the carbonyl group more susceptible to a nucleophilic attack by the *in situ*-generated organozinc intermediate.

In conclusion, we report a highly efficient catalytic one-pot process for Reformatsky and Barbier reactions, which was conveniently extended to the synthesis of 3-substituted-3-hydroxyindolin-2-ones from isatins.

Table 1. Effect of catalysts

Entry	Catalyst (mol%)	Time	Isolated yield (%)
1	$ZrCl_4$ (15)	20 min	40
2	$CpZrCl_3$(15)	15 min	60
3	$ZrOCl_2$ (15)	2 h	35
4	Cp_2ZrCl_2 (15)	5 min	87
5	Cp_2ZrCl_2 (10)	5 min	85
6	Cp_2ZrCl_2 (5)	15 min	62
7	Cp_2ZrCl_2 (0)	12 h	Trace

Temperature, 25 °C; solvent, DMF.

Table 2. Effect of metals

Entry	Solvent	Time	Isolated yield (%)
1	Fe dust	12 h	40
2	Mg dust	5 h	48
3	Sn dust	8 h	32
4	Mn dust	30 min	70
5	Zn dust	5 min	85

Cp_2ZrCl_2, 10 mol%; temperature, 25 °C; solvent, DMF.

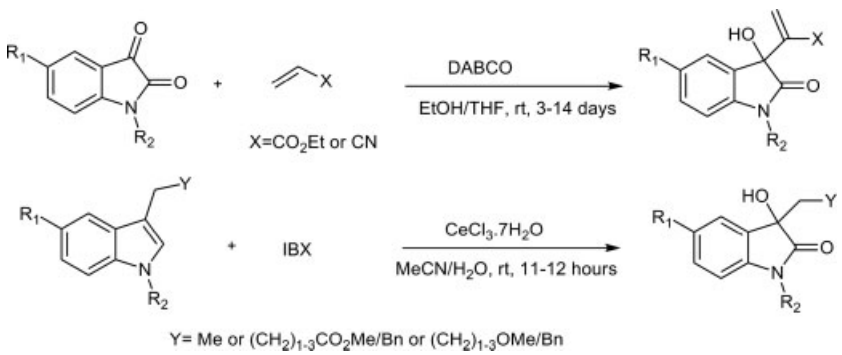
Table 3. Effect of solvents

Entry	Solvent	Time	Isolated yield (%)
1	THF	2.0 h	40
2	DME	3.5 h	28
3	DEE	2.5 h	32
4	DMF	5 min	85
5	Acetonitrile	5.0 h	32
6	Toluene	8.0 h	10
7	DCE	5.0 h	18

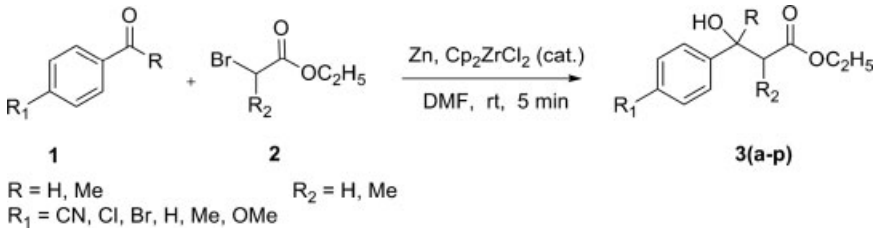
Cp_2ZrCl_2, 10 mol%; temperature, 25 °C.

Experimental

All isatin derivatives were synthesized according to the literature procedure.[41] Zirconium compounds, α-bromoester, benzyl bromides and metals (Fe, Mg, Sn, Mn, Zn) were purchased from



Scheme 1. Some of the reported methods for synthesis of 3-hydroxyindolin-2-ones.



Scheme 2. Cp_2ZrCl_2-catalyzed Reformatsky reaction.

Table 4. Reactions of aldehydes and ketones with α-haloesters

Entry	R	R_1	R_2	Product[a]	Isolated yield (%)	*Anti/Syn*[b]
1	H	H	H	**3a**	86	–
2	H	Cl	H	**3b**	85	–
3	H	CN	H	**3c**	79	–
4	H	CH_3	H	**3d**	82	–
5	H	OCH_3	H	**3e**	78	–
6	H	H	CH_3	**3f**	84	65/35
7	H	Cl	CH_3	**3g**	80	67/33
8	H	CH_3	CH_3	**3h**	85	67/33
9	CH_3	H	H	**3i**	76	–
10	CH_3	Cl	H	**3j**	78	–
11	CH_3	Br	H	**3k**	75	–
12	CH_3	CH_3	H	**3l**	70	–
13	CH_3	H	CH_3	**3m**	73	54/46
14	CH_3	Cl	CH_3	**3n**	80	53/47
15	CH_3	Br	CH_3	**3o**	77	56/44
16	CH_3	CH_3	CH_3	**3p**	72	52/48

[a] Spectral data compared with literature reports;[19–30] [b] *Anti/Syn* ratio was determined by ^{1}H NMR.

a commercial source and used as received. Solvents were distilled and dried before use. The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively on a Bruker Avance DPX 400 (400 MHz) spectrometer in $CDCl_3$/$(CD_3)_2SO$ using tetramethyl silane as an internal standard. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. High resolution mass spectra were recorded on a Bruker Maxix mass spectrometer. Melting points are uncorrected.

General Procedure

To a stirred solution of Cp_2ZrCl_2 (0.1 equiv.) and zinc (2.0 equiv.) in anhydrous DMF (5 ml) was added a solution of α-bromoester or benzyl bromide (1.5 equiv.) and *N*-methyl isatin (1.0 equiv.) in anhydrous DMF (5 ml) under nitrogen atmosphere at room temperature (25 °C) in a dropwise manner. After complete consumption of isatin as monitored by TLC, the reaction mixture was quenched with cold hydrochloric acid (20 ml, 1 M) and extracted with ethyl acetate. The organic layer was washed with water, then with aqueous solution of Na_2CO_3, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography on neutral alumina using a mixture of ethyl acetate and hexane (1 : 4) as the eluent to get the desired product.

*Ethyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetate (**6a**)*

White solid. M.p. 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.41 (d, J = 7.4 Hz, 1H, Ar–*H*), 7.32–7.36 (m, 1H, Ar–*H*), 7.07–7.11 (m, 1H, Ar–*H*), 6.83–6.85 (d, J = 7.8 Hz, 1H, Ar–*H*), 4.43 (s, 1H, -O*H*), 4.09–4.15 (m, 2H, -OCH_2-), 3.20 (s, 3H, N–CH_3), 2.93 (s, 2H, -CH_2-), 1.17–1.20 (t, J = 7.1 Hz, 3H, C–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1 (N–*C*=O), 170.3 (O–*C*=O), 143.5 (Ar–*C*), 130.1 (Ar–*C*), 129.2 (Ar–*C*), 123.8 (Ar–*C*), 123.1 (Ar–*C*), 108.5 (Ar–*C*), 73.5 (*C*–OH), 61.1(-OCH_2-), 41.2 (-CH_2-), 26.2 (N–CH_3), 13.9 (C–CH_3). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4Na$: 272.0899; found: 272.0917.

*Ethyl 2-(5-fluoro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetate (**6b**)*

White solid. M.p. 105–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.19 (m, 1H, Ar–*H*), 7.01–7.07 (m, 1H, Ar–*H*), 6.75–6.78 (m, 1H, Ar–*H*), 4.62 (s, 1H, -O*H*), 4.10–4.16 (m, 2H, -OCH_2-), 3.19 (s, 3H, N–CH_3), 2.93 (s, 2H, -CH_2-), 1.18–1.22 (t, J = 7.1 Hz, 3H, C–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 176.0 (N–*C*=O), 170.2 (O–*C*=O), 160.6 (Ar–*C*), 158.2 (Ar–*C*), 139.4 (Ar–*C*), 130.8 (Ar–*C*), 116.1 (Ar–*C*), 116.3 (Ar–*C*), 112.2 (Ar–*C*), 112.4 (Ar–*C*), 109.2 (Ar–*C*), 73.6 (*C*–OH), 61.2 (-OCH_2-), 41.1 (-CH_2-), 26.4 (N–CH_3), 13.9 (C–CH_3). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{14}FNO_4Na$: 290.0805; found: 290.0799.

*Ethyl 2-(5-chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetate (**6c**)*

White solid. M.p. 109–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.40 (d, J = 2.0 Hz, 1H, Ar–*H*), 7.30–7.33 (dd, J = 2.0 Hz, 8.3 Hz, 1H, Ar–*H*), 6.76–6.78 (d, J = 8.3 Hz, 1H, Ar–*H*), 4.57 (s, 1H, -O*H*), 4.10–4.16 (m, 2H, -OCH_2-), 3.19 (s, 3H, N–CH_3), 2.93 (s, 2H, -CH_2-), 1.19–1.22 (t, J = 7.2 Hz, 3H, C–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (N–*C*=O), 170.1 (O–*C*=O), 142.1 (Ar–*C*), 130.8 (Ar–*C*), 130.0 (Ar–*C*), 128.5 (Ar–*C*), 124.6 (Ar–*C*), 109.5 (Ar–*C*), 73.4 (*C*–OH), 61.3 (-OCH_2-), 41.0 (-CH_2-), 26.4 (N–CH_3), 13.9 (C–CH_3). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{14}ClNO_4Na$: 306.0509; found: 306.0504.

*Ethyl 2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)acetate (**6d**)*

White solid. M.p. 118–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.41 (d, J = 7.3 Hz, 1H, Ar–*H*), 7.17–7.39 (m, 6H, Ar–*H*), 7.01–7.05 (m, 1H, Ar–*H*), 6.69–6.71 (d, J = 7.8 Hz, 1H, Ar–*H*), 4.84–4.89 (m, 3H, N–CH_2–Ar, -O*H*), 4.06–4.09 (m, 2H, -OCH_2-), 2.98–3.09 (m, 2H, -CH_2-), 1.10–1.14 (t, J = 7.1 Hz, 3H, C–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5 (N–*C*=O), 170.1 (O–*C*=O), 142.7 (Ar–*C*), 135.4 (Ar–*C*), 130.0 (Ar–*C*), 129.4 (Ar–*C*), 128.8 (Ar–*C*), 127.7 (Ar–*C*), 127.3 (Ar–*C*), 123.9 (Ar–*C*), 123.2 (Ar–*C*), 109.6 (Ar–*C*), 73.5 (*C*–OH), 61.1 (-OCH_2-), 43.8 (N–CH_2–Ar), 41.4 (-CH_2-), 13.9 (C–CH_3). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{19}NO_4Na$: 348.1212; found: 348.1206.

Scheme 3. Cp_2ZrCl_2-catalyzed reactions of isatins with organic halides.

Table 5. Reactions of isatins with α-bromoesters and benzylbromides

Entry	R	R_1	R_2	Product	Isolated yield (%)
1	H	CH_3	$CO_2C_2H_5$	**6a**	80
2	F	CH_3	$CO_2C_2H_5$	**6b**	73
3	Cl	CH_3	$CO_2C_2H_5$	**6c**	82
4	H	$CH_2C_6H_5$	$CO_2C_2H_5$	**6d**	75
5	F	$CH_2C_6H_5$	$CO_2C_2H_5$	**6e**	80
6	Cl	$CH_2C_6H_5$	$CO_2C_2H_5$	**6f**	73
7	H	H	C_6H_5	**6g**	75
8	H	H	*p*-ClC_6H_4	**6h**	72
9	H	H	*p*-$CH_3C_6H_4$	**6i**	83
10	H	CH_3	C_6H_5	**6j**	80
11	H	CH_3	*p*-ClC_6H_4	**6k**	82
12	H	CH_3	*p*-$CH_3C_6H_4$	**6l**	82
13	Cl	CH_3	C_6H_5	**6m**	77
14	Cl	CH_3	*p*-ClC_6H_4	**6n**	76
15	Cl	CH_3	*p*-$CH_3C_6H_4$	**6o**	80

*Ethyl 2-(1-benzyl-5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acetate (**6e**)*

White solid. M.p. 119–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.35 (m, 5H, Ar–*H*), 7.17–7.19 (m, 1H, Ar–*H*), 6.88–6.94 (m, 1H, Ar–*H*), 6.61–6.64 (m, 1H, Ar–*H*), 4.84–4.95 (dd, *J* = 15.7 Hz, 23.5 Hz, 2H, N–CH_2–Ar), 4.68 (s, 1H, -O*H*), 4.11–4.19 (m, 2H, -OCH_2-), 3.01 (s, 2H, -CH_2-), 1.18–1.21 (t, *J* = 7.1 Hz, 3H, C–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2 (N–*C*=O), 170.1 (O–*C*=O), 160.6 (Ar–*C*), 158.2 (Ar–*C*), 138.5 (Ar–*C*), 135.0 (Ar–*C*), 130.9 (Ar–*C*), 130.8 (Ar–*C*), 128.8 (Ar–*C*), 127.8 (Ar–*C*), 127.2 (Ar–*C*), 116.3 (Ar–*C*), 116.1 (Ar–*C*), 112.4 (Ar–*C*), 112.1 (Ar–*C*), 110.3 (Ar–*C*), 73.7 (*C*–OH), 61.3 (-OCH_2-), 44.0 (N–CH_2–Ar), 41.2 (-CH_2-), 13.9 (C–CH_3). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{18}FNO_4Na$: 366.1118; found: 366.1112.

*Ethyl 2-(1-benzyl-5-chloro-3-hydroxy-2-oxoindolin-3-yl)acetate (**6f**)*

White solid. M.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.41 (d, *J* = 1.4 Hz, 1H, Ar–*H*), 7.27–7.35 (m, 5H, Ar–*H*), 7.17–7.20 (d, *J* = 8.3 Hz, 1H, Ar–*H*), 6.62–6.64 (d, *J* = 8.3 Hz, 1H, Ar–*H*), 4.84–4.94 (dd, *J* = 15.7 Hz, 24.7 Hz, 2H, N–CH_2–Ar), 4.57 (s, 1H, -O*H*), 4.11–4.22 (m, 2H, -OCH_2-), 2.99 (s, 2H, -CH_2-), 1.20–1.23 (t, *J* = 7.1 Hz, 3H, C–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9 (N–*C*=O), 170.1 (O–*C*=O), 141.2 (Ar–*C*), 134.8 (Ar–*C*), 130.9 (Ar–*C*), 129.9 (Ar–*C*), 128.9 (Ar–*C*), 128.6 (Ar–*C*), 127.8 (Ar–*C*), 127.2 (Ar–*C*), 124.6 (Ar–*C*), 110.7 (Ar–*C*), 73.5 (*C*–OH), 61.4 (-OCH_2-), 44.0 (N–CH_2–Ar), 41.1 (-CH_2-), 13.9 (C–CH_3). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{18}ClNO_4Na$: 382.0822; found: 382.0842.

*3-Benzyl-3-hydroxyindolin-2-one (**6g**)*

White solid. M.p. 172–175 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 10.05 (bs, 1H, -N*H*-C=O), 7.05–7.14 (m, 5H, Ar–*H*), 6.88–6.93 (m, 3H, Ar–*H*), 6.59–6.65 (m, 1H, Ar–*H*), 6.14 (s, 1H, -O*H*), 3.14–3.17 (d, *J* = 12.6 Hz, 1H, C–CH_2–Ar), 2.99–3.02 (d, *J* = 12.6 Hz, 1H, C–CH_2–Ar). ^{13}C NMR (100 MHz, DMSO-d^6): δ 179.2 (N–*C*=O), 142.0 (Ar–*C*), 135.4 (Ar–*C*), 131.3 (Ar–*C*), 130.5 (Ar–*C*), 129.4 (Ar–*C*), 127.9 (Ar–*C*), 126.8 (Ar–*C*), 125.0 (Ar–*C*), 121.7 (Ar–*C*), 109.7 (Ar–*C*), 77.1 (*C*–OH), 43.8 (C–CH_2–Ar). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{13}NO_2Na$: 262.0844; found: 262.0857.

*3-(4-Chlorobenzyl)-3-hydroxyindolin-2-one (**6h**)*

White solid. M.p. 224–226 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 10.08 (bs, 1H, -N*H*-C=O), 7.08–7.15 (m, 4H, Ar–*H*), 6.88–6.92 (m, 3H, Ar–*H*), 6.60–6.62 (d, *J* = 7.6 Hz, 1H, Ar–*H*), 6.18 (s, 1H, -O*H*), 3.11–3.14 (d, *J* = 12.6 Hz, 1H, C–CH_2–Ar), 2.95–2.98 (d, *J* = 12.6 Hz, 1H, C–CH_2–Ar). ^{13}C NMR (100 MHz, DMSO-d^6): δ 178.5 (N–*C*=O), 141.4 (Ar–*C*), 134.0 (Ar–*C*), 131.8 (Ar–*C*), 131.0 (Ar–*C*), 130.6 (Ar–*C*), 128.9 (Ar–*C*), 127.4 (Ar–*C*), 124.4 (Ar–*C*), 121.3 (Ar–*C*), 109.3 (Ar–*C*), 76.3 (*C*–OH), 42.5 (C–CH_2–Ar). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{12}ClNO_2Na$: 296.0454; found: 296.0452.

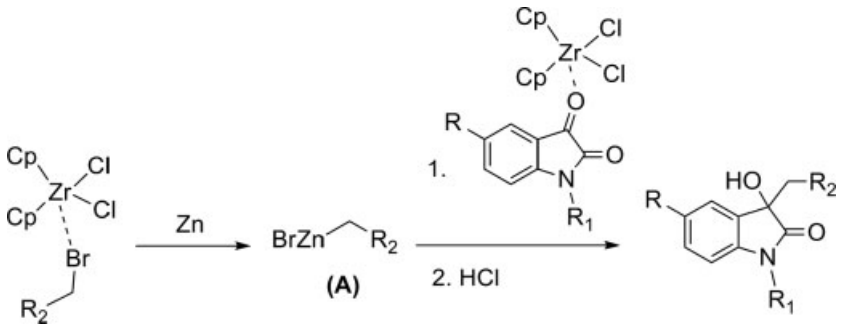


Figure 2. Plausible mechanism for Cp_2ZrCl_2-catalysed reaction.

*3-Hydroxy-3-(4-methylbenzyl)indolin-2-one (**6i**)*

White solid. M.p. 185–188 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 10.08 (bs, 1H, -N*H*-C=O), 7.21–7.23 (d, J = 7.2 Hz, 1H, Ar–*H*), 7.15–7.19 (m, 1H, Ar–*H*), 6.90–7.00 (m, 3H, Ar–*H*), 6.80–6.82 (d, J = 8.0 Hz, 2H, Ar–*H*), 6.65–6.67 (d, J = 7.6 Hz, 1H, Ar–*H*), 6.18 (s, 1H, -O*H*), 3.15–3.18 (d, J = 12.6 Hz, 1H, C–CH_2–Ar), 3.02–3.05 (d, J = 12.6 Hz, 1H, C–CH_2–Ar), 2.22 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, DMSO-d^6): δ 179.2 (N–*C*=O), 142.0 (Ar–*C*), 135.7 (Ar–*C*), 132.2 (Ar–*C*), 131.4 (Ar–*C*), 130.3 (Ar–*C*), 129.3 (Ar–*C*), 128.5 (Ar–*C*), 124.9 (Ar–*C*), 121.7 (Ar–*C*), 109.7 (Ar–*C*), 77.1 (*C*–OH), 43.4 (C–CH_2–Ar), 20.9 (Ar–CH_3). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{15}NO_2Na$: 276.1000; found: 276.1015.

*3-Benzyl-3-hydroxy-1-methylindolin-2-one (**6j**)*

White solid. M.p. 162–165 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 7.20–7.21 (t, J = 1.3 Hz, 1H, Ar–*H*), 7.13–7.14 (d, J = 0.8 Hz, 1H, Ar–*H*), 7.06–7.07 (m, 3H, Ar–*H*), 6.98–6.99 (t, J = 0.8 Hz, 1H, Ar–*H*), 6.83–6.86 (m, 2H, Ar–*H*), 6.74–6.76 (d, J = 7.7 Hz, 1H, Ar–*H*), 6.21 (s, 1H, -O*H*), 3.15–3.18 (d, J = 7.6 Hz, 1H, C–CH_2–Ar), 3.00–3.03 (d, J = 7.6 Hz, 1H, C–CH_2–Ar), 2.89 (s, 3H, N–CH_3). ^{13}C NMR (100 MHz, DMSO-d^6): δ 182.2 (N–*C*=O), 148.1 (Ar–*C*), 140.0 (Ar–*C*), 135.4 (Ar–*C*), 135.1 (Ar–*C*), 134.1 (Ar–*C*), 132.6 (Ar–*C*), 131.6 (Ar–*C*), 129.3 (Ar–*C*), 127.1 (Ar–*C*), 113.2 (Ar–*C*), 81.7 (*C*–OH), 48.8 (C–CH_2–Ar), 30.7 (N–CH_3). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{15}NO_2Na$: 276.1000; found: 276.1025.

*3-(4-Chlorobenzyl)-3-hydroxy-1-methylindolin-2-one (**6k**)*

White solid. M.p. 182–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.31 (m, 1H, Ar–*H*), 7.18–7.19 (d, J = 0.8 Hz, 1H, Ar–*H*), 7.06–7.12 (m, 3H, Ar–*H*), 6.87–6.90 (m, 2H, Ar–*H*), 6.67–6.69 (d, J = 7.8 Hz, 1H, Ar–*H*), 3.38 (s, 1H, -O*H*), 3.27–3.30 (d, J = 13.0 Hz, 1H, C–CH_2–Ar), 3.11–3.15 (d, J = 13.0 Hz, 1H, C–CH_2–Ar), 3.03 (s, 3H, N–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5 (N–*C*=O), 143.1 (Ar–*C*), 132.8 (Ar–*C*), 132.5 (Ar–*C*), 131.5 (Ar–*C*), 129.8 (Ar–*C*), 128.9 (Ar–*C*), 127.9 (Ar–*C*), 124.3 (Ar–*C*), 122.9 (Ar–*C*), 108.4 (Ar–*C*), 76.69 (*C*–OH), 44.1 (C–CH_2–Ar), 26.0 (N–CH_3). HRMS (ESI): m/z [M + Na]$^+$ calcd For $C_{16}H_{14}ClNO_2Na$: 310.0611; found: 310.0632.

*3-Hydroxy-1-methyl-3-(4-methylbenzyl)indolin-2-one (**6l**)*

White solid. M.p. 149–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.29 (m, 1H, Ar–*H*), 7.19–7.21 (m, 1H, Ar–*H*), 7.04–7.08 (m, 1H, Ar–*H*), 6.93–6.95 (d, J = 8.0 Hz, 2H, Ar–*H*), 6.83–6.86 (d, J = 8.0 Hz, 2H, Ar–*H*), 6.66–6.68 (d, J = 7.8 Hz, 1H, Ar–*H*), 3.43 (s, 1H, -O*H*), 3.27–3.30 (d, J = 13.0 Hz, 1H, C–CH_2–Ar), 3.11–3.14 (d, J = 13.0 Hz, 1H, C–CH_2–Ar), 3.03 (s, 3H, N–CH_3), 2.26 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9 (N–*C*=O), 143.2 (Ar–*C*), 136.3 (Ar–*C*), 130.8 (Ar–*C*), 130.3 (Ar–*C*), 130.1 (Ar–*C*), 129.4 (Ar–*C*), 128.4 (Ar–*C*), 124.4 (Ar–*C*), 122.7 (Ar–*C*), 108.1 (Ar–*C*), 76.7 (*C*–OH), 44.3 (C–CH_2–Ar), 25.9 (N–CH_3), 21.0 (Ar–CH_3). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{17}NO_2Na$: 290.1157; found: 290.1181.

*3-Benzyl-5-chloro-3-hydroxy-1-methylindolin-2-one (**6m**)*

White solid. M.p. 165–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12–7.24 (m, 5H, Ar–*H*), 6.94–6.97 (m, 2H, Ar–*H*), 6.55–6.57 (d, J = 8.2 Hz, 1H, Ar–*H*), 3.97 (s, 1H, -O*H*), 3.29–3.32 (d, J = 12.9 Hz, 1H, C–CH_2–Ar), 3.17–3.20 (d, J = 12.9 Hz, 1H, C–CH_2–Ar), 2.97 (s, 3H, N–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6 (N–*C*=O), 141.6 (Ar–*C*), 133.5 (Ar–*C*), 131.0 (Ar–*C*), 130.1 (Ar–*C*), 129.4 (Ar–*C*), 128.3 (Ar–*C*), 127.8 (Ar–*C*), 127.0 (Ar–*C*), 124.9 (Ar–*C*), 109.1 (Ar–*C*), 76.71 (*C*–OH), 44.9 (C–CH_2–Ar), 26.0 (N–CH_3). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{14}ClNO_2Na$: 310.0611; found: 310.0616.

*5-Chloro-3-(4-chlorobenzyl)-3-hydroxy-1-methylindolin-2-one (**6n**)*

White solid. M.p. 179–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08–7.12 (d, J = 8.4 Hz, 2H, Ar–*H*), 6.85–6.87 (d, J = 8.4 Hz, 2H, Ar–*H*), 6.57–6.59 (d, J = 8.2 Hz, 1H, Ar–*H*), 7.21–7.26 (m, 2H, Ar–*H*), 3.92 (s, 1H, -O*H*), 3.23–3.26 (d, J = 12.9 Hz, 1H, C–CH_2–Ar), 3.14–3.17 (d, J = 12.9 Hz, 1H, C–CH_2–Ar), 2.98 (s, 3H, N–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3 (N–*C*=O), 141.5 (Ar–*C*), 133.0 (Ar–*C*), 131.9 (Ar–*C*), 131.4 (Ar–*C*), 130.7 (Ar–*C*), 129.6 (Ar–*C*), 128.5 (Ar–*C*), 128.0 (Ar–*C*), 124.8 (Ar–*C*), 109.3 (Ar–*C*), 76.70 (*C*–OH), 44.1 (C–CH_2–Ar), 26.1 (N–CH_3). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{13}Cl_2NO_2Na$: 344.0221; found: 344.0222.

*5-Chloro-3-hydroxy-1-methyl-3-(4-methylbenzyl)indolin-2-one (**6o**)*

White solid. M.p. 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.25 (dd, J = 2.0 Hz, 8.2 Hz, 1H, Ar–*H*), 7.18–7.19 (d, J = 2.0 Hz, 1H, Ar–*H*), 6.95–6.97 (d, J = 7.8 Hz, 2H, Ar–*H*), 6.84–6.86 (d, J = 7.8 Hz, 2H, Ar–*H*), 6.58–6.60 (d, J = 8.3 Hz, 1H, Ar–*H*), 3.34 (s, 1H, -O*H*), 3.23–3.26 (d, J = 13.0 Hz, 1H, C–CH_2–Ar), 3.11–3.14 (d, J = 13.0 Hz, 1H, C–CH_2–Ar), 3.01 (s, 3H, N–CH_3), 2.30 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4 (N–*C*=O), 141.7 (Ar–*C*), 136.6 (Ar–*C*), 131.0 (Ar–*C*), 130.2 (Ar–*C*), 130.0 (Ar–*C*), 129.4 (Ar–*C*), 128.6 (Ar–*C*), 128.2 (Ar–*C*), 124.9 (Ar–*C*), 109.1 (Ar–*C*), 76.69 (*C*–OH), 44.4 (C–CH_2–Ar), 26.0 (N–CH_3), 21.0 (Ar–CH_3). HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{16}ClNO_2Na$: 324.0767; found: 324.0762.

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