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Selective and efficient synthesis of 3-indolyl-2-oxindoles under catalysis of $LiClO_4$

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ABSTRACT

An efficient and convenient protocol for synthesis of 3-hydroxy-3-indolyl-2-oxindoles and 3,3-diindolyl-2-oxindoles is presented here. The syntheses were achieved selectively under catalysis of $LiClO_4$ whereby the products were obtained purely.

Keywords: *Lithium perchlorate, 3-hydroxy-3-indolyl-2-oxindole, 3,3-diindolyl-2-oxindole, Selective synthesis.*

1. Introduction

Indole is a prevalent heterocyclic nucleus existing in many natural products possessing diverse physiological activities [1]. 3,3-Diaryl-2-oxindoles are recurrent motifs in the domain of clinical drugs and biologically active compounds such as anti-proliferatives, anti-bacterials, anti-protozoals and anti-inflammatory agents [2]. They have also been used as laxatives [3] and lead molecules for development of drugs to facilitate Ca^{2+} depletion mediated inhibition of translation initiation [4]. In addition, a large number of diindolylmethanes, such as vibrindole A, isolated from natural sources [5] have shown promising biological activities [6]. A large members of synthetic indoles were derived from isatin, a privileged lead molecule and a reactive substrate for many syntheses. Isatin derivatives were shown to have a broad spectrum of bioactivity as many of which were identified as anti-HIV, [7] antiviral [8], anti-tumor [9,10], anti-fungal [11,12], anti-angiogenic [13], anti-convulsants [14], anti-parkinson's disease therapeutic [15] and effective SARS coronavirus 3cl protease inhibitor [16]. These interesting properties have drawn many efforts towards the synthesis and pharma-cological screening of isatin derivatives. During these investigations, the indolin-2-one (oxindole) moiety has been recognized as a biologically active framework [17,18]. Thus, it is not surprising that access to several members of this class is the goal of many research laboratories.

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Oxindole derivatives have been prepared by reaction of isatin or its derivatives with barbituric acid [19], aromatics in triflic acid [20], pyrazolones [21] and many other routes [22-25]. The 3,3-Di-(indol-3-yl) indolin-2-ones are prepared by the reaction of isatin and indoles in acidic conditions and several methods have been developed for synthesis of these compounds [26,27]. On the other hand, a number of oxindole alkaloids having a hydroxyl functionality at the C-3 position possess various bioactivities [28,29] and are synthesized by a variety of methods [25,30,31].

2. Experimental

*2.1. Preparation of 3-(indol-3-yl)-3-hydroxyindolin-2-one (**3a**)*

To a mixture of isatin (0.14 g, 1 mmol) and indole (0.11 g, 1 mmol) placed in a vial was added a solution of $LiClO_4$ (0.01 g, 10 mol%) in ethanol (95%, 2 mL). The vial was heated in an oil bath at 60 °C. Progress of the reaction was monitored by TLC on silica gel (Merck, 60 GF_{254}) coated aluminum sheets using ethyl acetate / petroleum ether in the ratio of 8:12 as eluents. After 4 hours the reaction was completed and gave the product **3a** solely which was appeared as a light brown point on TLC. The product which precipitated from ethanol solution was filtered and dried at 50 °C. The identity and purity of the product was checked by measuring and comparison of its melting point and spectroscopic data with those reported in literature.

*2.2. Synthesis of symmetrical 3,3-di(indol-3-yl)indolin-2-ones (**4a**)*

To a mixture of isatin (0.14 g, 1 mmol) and indole (0.22 g, 2 mmol) placed in a vial was added a solution of $LiClO_4$ (0.02 g, 20 mol%) in ethanol (95%, 2 mL). The vial was heated in an oil bath at 60 °C. Progress of the reaction was monitored by TLC on silica gel (Merck, 60 GF_{254}) coated aluminum sheets using ethyl acetate / petroleum ether in the ratio of 3:4 as eluents. After 4 hours the reaction was completed and gave the product (**4a**) solely which was appeared as a light brown point on TLC. The product precipitated during the reaction from ethanol solution was filtered and dried in oven at 50 °C. The identity and purity of the product was checked by measuring and comparison of its melting point and spectroscopic data with those reported in literature.

Selected spectral data:

*3-Hydroxy-3-(1H-indol-3-yl) indolin-2-one **(3a)***: White solid. IR (KBr): $\bar{\nu}$ = 3457, 3261, 1702, 1618, 1476, 1182. ^{1}HNMR [DMSO, 300 MHz]: δ= 6.32 (1H, s, OH), 6.85 (1H, t, *J*= 8.0 Hz), 6.90 (1H, d, *J*= 7.6 Hz), 6.96 (1H, t, *J*= 6.7 Hz), 7.02 (1H, t, *J*= 7.0 Hz), 7.06 (1H, d, *J*= 2.6 Hz), 7.23 (1H, d, *J*= 6.0 Hz), 7.25 (1H, t, *J*= 6.5 Hz), 7.32 (1H, d, *J*= 8.2 Hz), 7.34 (1H, d, *J*= 9.4 Hz), 10.32 (1H, s, N-H), 10.97 (1H, br, N-H).

*5-Bromo-3-hydroxy-3-(2-methyl-1H-indol-3-yl) indolin -2-one **(3f)***: Brown solid. IR (KBr): $\bar{\nu}$ = 3387 (br), 1721, 1615, 1465, 1178. ^{1}H NMR [DMSO, 300 MHz]: δ= 2.41 (3H, s, CH_3), 6.47 (1H, s, OH), 6.77 (1H, t, *J*= 7.5 Hz, 5′-H), 6.86-6.98 (3H, m), 7.21 (1H, d, *J*= 8.1 Hz, H-7), 7.24 (1H, d, *J*= 2.0 Hz, 4-H), 7.41 (1H, dd, *J*= 8.1 and 2.0 Hz, 6-H), 10.54 (1H, s, N-H), 10.95 (1H, s, N-H).

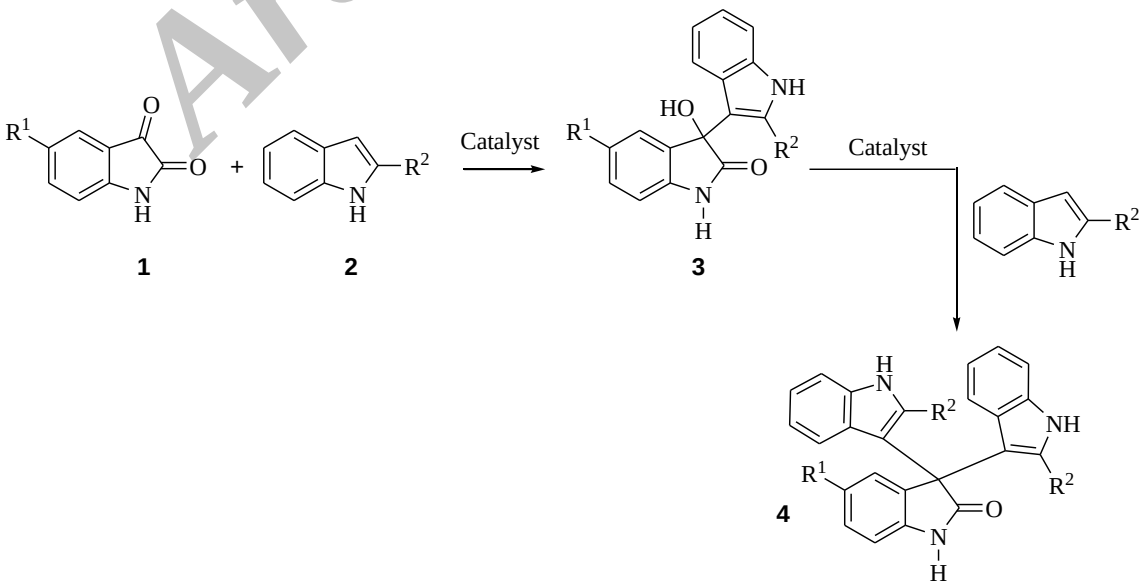
*3,3-di(1H-indol-3-yl)indolin-2-one **(4a)***: White solid. IR (KBr): $\bar{\nu}$ = 3420, 3300, 1704, 1610, 1105, 737. ^{1}H NMR [DMSO, 500 MHz]: δ= 6.79 (2H, t, *J*= 7.7 Hz), 6.84 (2H, d, *J*= 2.2 Hz, 2′-H of indoles), 6.92 (1H, t, *J*= 7.5 Hz), 6.97-7.02 (3H, m), 7.22 (4H, d, *J*= 7.8 Hz), 7.35 (2H, d, *J*= 8.1 Hz), 10.58 (1H, s, N-H), 10.94 (2H, br, N-H).

*5-Nitro- 3,3-di (1-methyl-1H-indol-3-yl) indolin-2-one **(4c)***: Pale brown solid. IR (KBr): $\bar{\nu}$ = 3230, 3105, 3055, 1715, 1608, 1465, 1325, 1158, 730. ^{1}H NMR [DMSO, 500 MHz]: δ= 3.72 (6H, s, $2CH_3$), 6.89 (2H, t, *J*= 7.5 Hz, 5′-H of indoles), 7.02 (2H, s, 2′-H of indoles), 7.11 (2H, t, *J*= 7.5 Hz, 6′-H of indoles), 7.21 (1H, d, *J*= 8.6 Hz, 7-H), 7.26 (2H, d, *J*= 8.1 Hz), 7.40 (2H, d, *J*= 8.2 Hz), 8.00 (H, s, 4-H), 8.25 (1H, d, *J*= 8.6 Hz, 6-H), 11.36 (1H, s, N-H).

3. Results and Discussion

Indolylation of isatin is essentially a Friedel-Crafts electrophilic substitution reaction. Although, indole undergoes aromatic electrophilic substitutions about 10^{13} times faster than benzene, its addition onto isatin carbonyl group still needs suitable catalysts to proceed in a reasonable rate. So far, many catalysts have been introduced for this electrophilic substitution reaction to address additional concerns such as recoverability and prevention of environment pollution. However, most of the easily recoverable catalysts are heterogeneous, and because the reactions are catalyzed on their surface usually give rise to less selectivity [32].

On the other hand, it has been proven that the reaction of isatin **1** and indole **2** pass through two acid demanding steps to afford 3-hydroxy-3-indolyl-2-oxindole **3** and 3,3-diindolyl-2-oxindole **4**, respectively (Scheme 1).

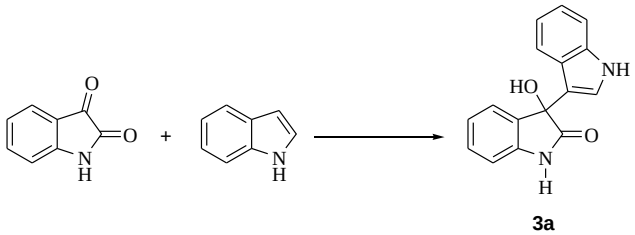


Scheme 1. The two consecutive Friedel-Crafts reactions between isatins and indoles.

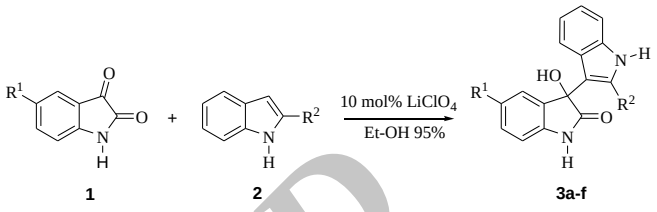
Strong acidic catalysts are able to catalyze both steps of indolylation and directly give the 3,3-diindolyl-2-oxindoles. Thus, restriction of this reaction at its first step, to produce only 3-hydroxy-3-indolyl-2-oxindole derivatives **3**, would need moderate and homogeneous catalysts to be applied. In this view and following our interest in synthesis of 3-hydroxy-3-indolyl-2-oxindole **3**, we led to examine $LiClO_4$ as a catalyst for controlling the reaction of indoles with isatin derivatives. To test this hypothesis and find out the optimal conditions, a mixture of equal quantities (1 mmol) of indole and isatin was initially chosen as the model reaction. For this model reaction (scheme 2), the effects of different variables such as temperature, solvent and amounts of the catalyst were evaluated in terms of reaction times and yields of the products. Results of these experiments were shown in Table 1.

We were delighted with sole formation of product **3a** from the model reaction using 10 mol% $LiClO_4$ at 60 °C in ethanol (95%). $LiC1O_4$ has a moderate acidic activity in ethanol which makes it a useful catalyst for selective synthesis of compounds **3**. As Table 1 shows, increasing either the amount of catalyst to more than 10 mol% or the temperature to above 60 °C facilitate the formation of 3,3-biindolyl-2-oxindole and give rise to a mixture of the products **3** and **4**. After determining 10 mol% of $LiClO_4$ in ethanol 95% at 60 °C as an optimal condition (scheme 3) we set out to examine the substrate scope of this methodology by employing several derivatives of isatin and indole in the same condition.

As Table 2 shows, this method is equally applicable for synthesis of several 3-hydroxy-3-indolyl-2-oxindole derivatives.



Scheme 2. The model reaction between isatin and indole.



Scheme 3. Synthesis of 3-hydroxy-3-indolyl-2-oxindoles under the optimal conditions.

Likely, the lithium cations which are partially tethered by ethanol molecules serve as Lewis acid and coordinate with isatin carbonyl group to increase its electrophilic tendency (Scheme 4). Nucleophilic attack of indole to the activated carbonyl group of isatin results in addition to this group and formation of the product **3**.

By studying Table 1 carefully and distinguishing the ability of $LiClO_4$ for catalysis of 3,3-diindolyl-2-oxindoles formation under some conditions, we envisaged to set up a proper condition by adopting the catalyst system for such synthesis.

As we expected, the reaction of 2 mmol indole and 1 mmol isatin was easily carried out by using 20 mol% of $LiClO_4$ in ethanol at 60 °C and after 4 h, the corresponding product of 3,3-diindolyl-2-oxindole

Table 1. Results of optimization experiments performed on the model reaction of indole (1 mmol) and isatin (1 mmol).

Entry	Solvent	$LiClO_4$ (mol%)	Temperature (°C)	Yield (%)[a]	Time (h)
1	THF	10	60	Mixture[b]	4
2	EtOH	10	60	Mixture[b]	6
3	EtOH	10	60	93	4
4	EtOH	10	25	35	6
5	EtOH	20	60	Mixture[b]	4
6	EtOH	10	80	Mixture[b]	4
7	CH_3CN	10	60	Mixture[b]	5
8	H_2O	10	60	50	4
9	CH_2Cl_2	10	60	10	4

[a]Yields of isolated product.
[b]A mixture of products **3a** and **4a** is formed.

Table 2. The 3-hydroxy-3-indolyl-2-oxindole adducts formed from reaction of selected isatins and indoles.

Product	R^1	R^2	Yield (%)[a]	Time (h)	m.p. (°C)	Lit. m.p. (°C)	Ref.
3a	H	H	93	4	>300	294-296	[34]
3b	H	Me	91	4	176-178	178-180	[34]
3c	Cl	Me	87	3.5	175-177	174-176	[33]
3d	Cl	H	88	3.5	205-207	206-208	[33]
3e	Br	H	85	4	188-200	200	[34]
3f	Br	Me	82	4	137-139	136-138	[34]

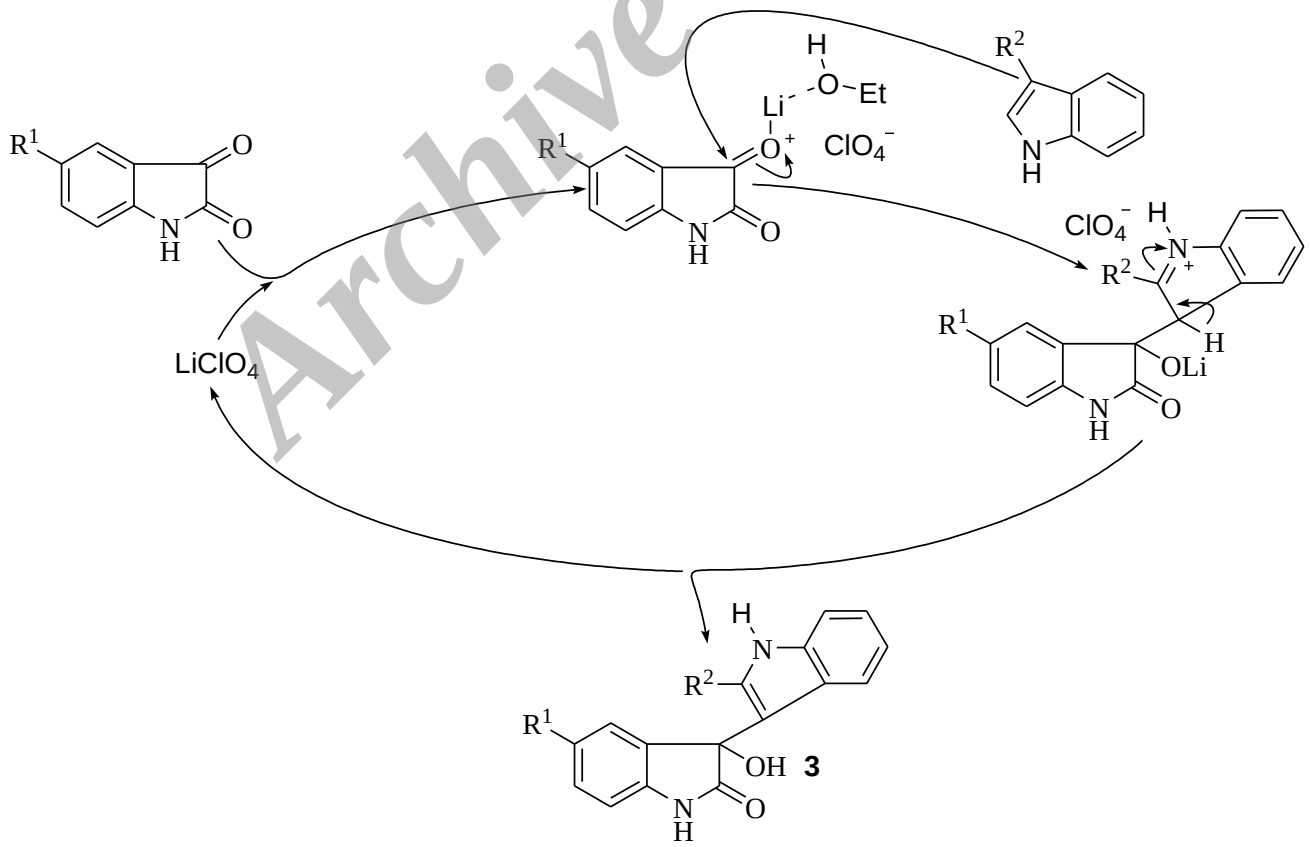
[a] Yields of isolated products.

(**4a)** was obtained in fairly high yield (Table 3, entry 1). Encouraged by this success we aimed to explore the reliability of this method by applying a variety of indoles and isatins (Scheme 5).

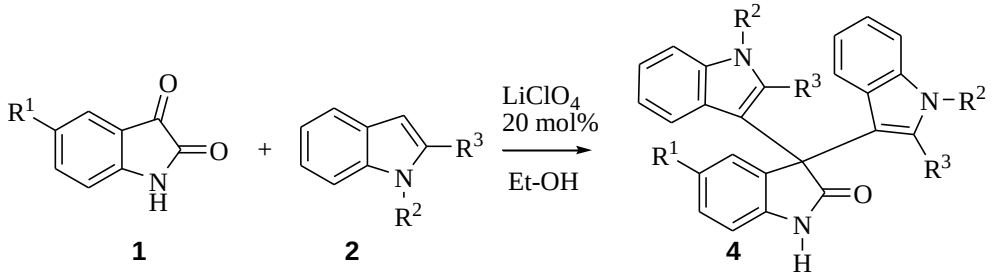
As was summarized in Table 3, a range of substrates are applicable to this method for synthesis of relevant 3,3-diindolyl-2-oxindoles.Based on these observations, it can be concluded that production of 3-hydroxy-3-indolyl-2-oxindoles under $LiClO_4$ catalysis is much faster than formation of 3,3-diindolyl-2-oxindoles.

As was shown in Scheme 6, the reaction goes through initial formation of 3-hydroxy-3-indolyl-2-oxindole **3**, according to the mechanism depicted in Scheme 4.

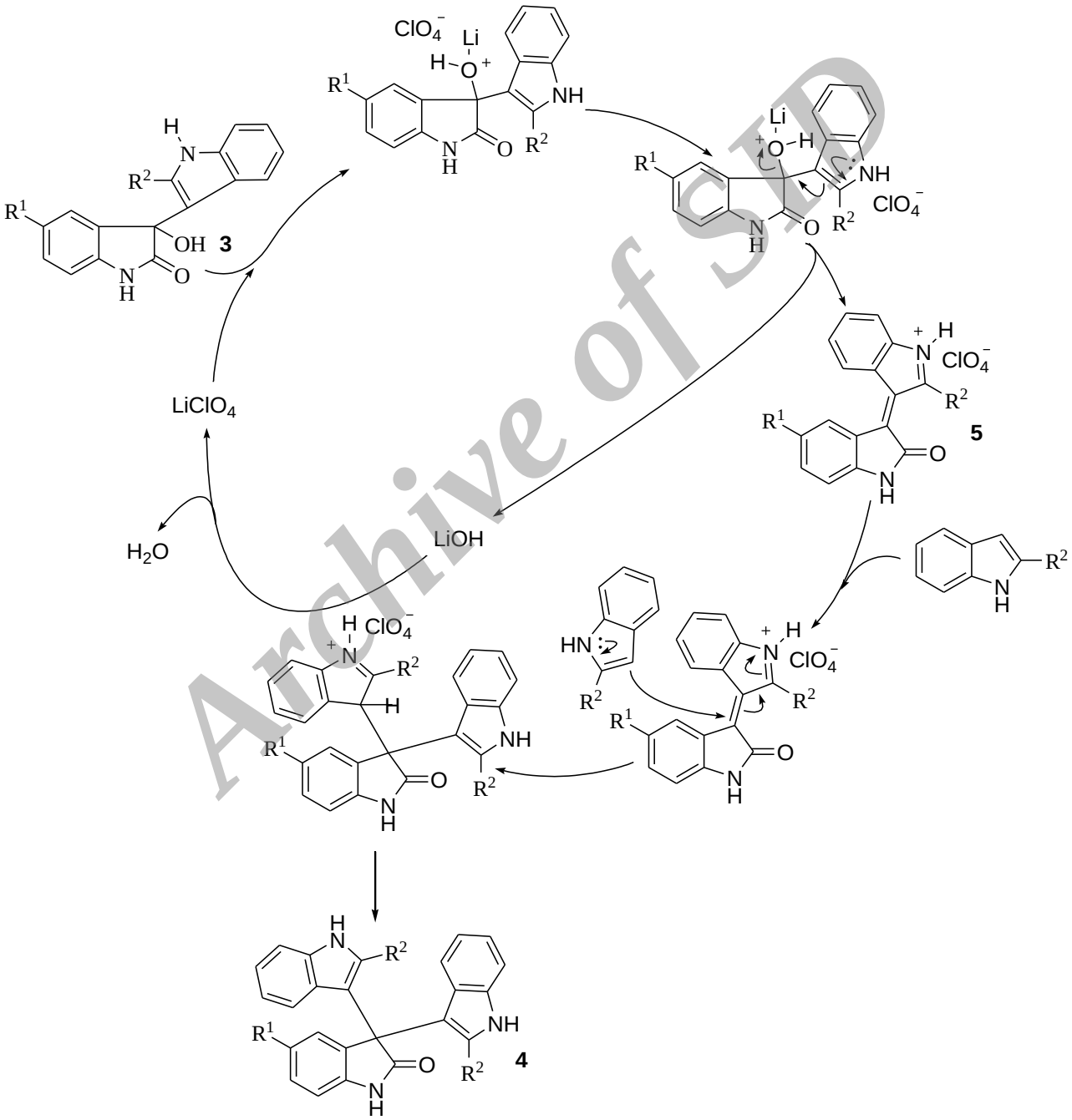
Coordination of the hydroxyl function of compound **3** with lithium cation makes this group more viable to leave the molecule. Upon the electron push of the lone pair of indole nitrogen the compound **3** liberates a LiOH molecule to form an azafulvalene intermediate **5**, which due to strong electrophilicity undergoes a subsequent conjugate addition with the second indole molecule to give the product of 3,3-diindolyl-2-oxindole **4**.



Scheme 4. A plausible mechanism for formation of 3-hydroxy-3-indolyl-2-oxindoles.



Scheme 5. Synthesis of 3,3-diindolyl-2-oxindoles under optimal conditions.



Scheme 6. A mechanistic pathway for formation of 3,3-diindolyl-2-oxindoles **4**.

Table 3. The 3,3-diindolyl-2-oxindoles synthesized from reaction of selected isatins and indoles.[a]

Product	R^1	R^2	R^3	Yield (%)[b]	Reaction time (h)	m.p. (°C)	Lit. m.p. (°C)	Ref.
4a	H	H	H	93	4	>300	311-313	[34]
4b	H	H	Me	90	4	297-299	300-301	[34]
4c	NO_2	Me	H	93	3.5	>300	>300	[34]
4d	Cl	Me	H	90	4.5	298-300	>300	[36]
4e	Cl	H	H	88	4.5	>300	298-300	[36]
4f	H	Me	H	91	4	298-300	301-303	[35]

[a]Reaction condition: 2 mmol indoles, 1 mmol isatins in ethanol at 60 °C.
[b]Yields of isolated products based on isatin derivatives.

4. Conclusions

Here we have introduced $LiClO_4$ as a mild and efficient catalyst for controlled synthesis of 3-hydroxy-3-indolyl-2-oxindoles in ethanol solution at 60 °C. A greater amount of the catalyst was also found useful for efficient production of 3,3-diindolyl-2-oxindoles at 60 °C in ethanol. The scopes of these methods were successfully examined by applying a variety of indoles and isatins.

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