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Catalyst-free synthesis of 3-hydroxy-3-(alkyl/aryl)indolin-2-ones by addition of organoaluminum reagents to isatins

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ABSTRACT

An efficient synthesis of 3-hydroxy-3-(alkyl/aryl)indol-2-one derivatives has been described by the reactions of isatin with organoaluminum reagents. The reaction is very rapid and yields are high. The protocol is applicable for substituted isatins as well as a variety of organoaluminums.

The 3-hydroxyoxindole moiety is found in many biologically active molecules such as convolutamydines.[1] This is important structural motif in proteasome inhibitors like TMC-95A/B.[2] The 3-hydroxyoxindole moiety is also found in various alkaloids such as donaxaridine, dioxibrassinine, welwitindolinone C, and 3-hydroxyglucoisatisin.[3] The carbon–carbon bond formation has been one of the most studied reactions in the past 10 years.[4] In these studies, the additions of organozinc to aldehydes are one of the most reliable processes and thus gain much attention from chemists.[5–9] Among alkylation reagents, trialkylaluminum reagents are more interesting since they are inexpensive and commercially available.[10] Among the organometallic species, organoaluminum reagents stand out for practical applications. The additional advantages of organoaluminum compounds include low toxicities and considerable stabilities.[11] The first example of the asymmetric addition of $AlEt_3$ to aldehydes, catalyzed by a Ti(IV)–BINOL complex, was developed by Chan et al. in 1997.[12d] Other reports include the titanium catalyzed addition of Me_3Al,[12b,c] Et_3Al,[12b] (allyl)$AlEt_2$[12b], and Ph_3Al[12a] to aldehydes. In addition to this some of the methods have been reported using nickel catalyzed Me_3Al[11] or $(Me_3Al)_2$–DABCO[11c] to aldehydes (Fig. 1).

Owing to the significance of this organoaluminum reagent motif, the development of these reactions is highly valuable, and the alkylation/arylation of isatins would be the most straightforward approach to this end. Catalyst free reactions have received special attention in recent years.[13] There are two methods for the synthesis of 3-hydroxy-3-alkyl/aryl-indolin-2-ones which involves using Grignard reagents (RMgX)[14] or arylboronic acids ($RB(OH)_2$).[15] Following our recent interest in the synthesis of new 3-hydroxy-

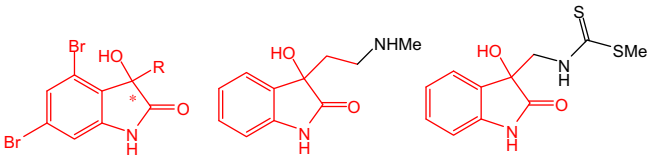
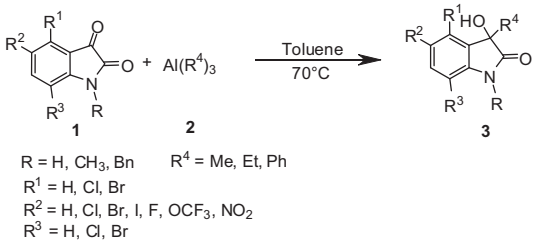


Figure 1. Representative examples of biologically active 3-hydroxy-indolin-2-ones.



Scheme 1. Synthesis of substituted 3-hydroxy-indolin-2-ones under catalyst-free condition.

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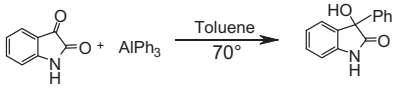
Table 1
Screened solvents for the reaction of isatin with organoaluminum reagents



Entry	Solvent	Condition[a]	Yield[b] (%)
1	DMSO	120 °C, 8 h	55
2	Toluene	rt, 24 h	20
3	Xylene	70 °C, 12 h	55
4	Toluene	70 °C, 3 h	90
5	Dioxane	100 °C, 12 h	40
6	Acetonitrile	Reflux, 12 h	20
7	THF	Reflux, 12 h	20
8	DCM	Reflux, 12 h	20

[a] Reaction conditions: isatin (1 equiv) and organoaluminum (2 equiv) in solvent stirred at stipulated time.
[b] Isolated yields.

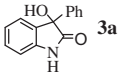
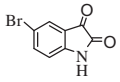
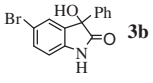
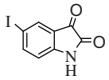
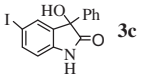
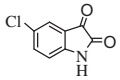
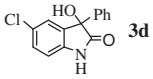
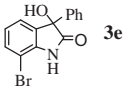
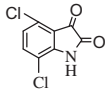
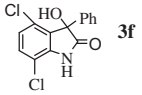
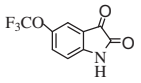
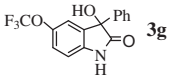
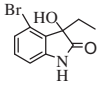
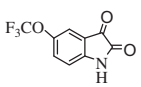
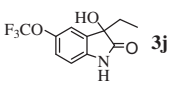
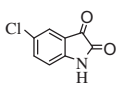
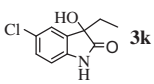
3-substituted oxindole,[16] herein, we wish to report the catalyst free efficient synthesis of 3-hydroxy-3-(alkyl/aryl)indolin-2-one derivatives by the organometallic reaction of isatins with trialkyl/aryl aluminum in excellent yields. To the best of our knowledge, however, there have been no examples reported to date that employ this strategy (Scheme 1).

We have initiated our investigation by examining the reaction between free isatin **1** and triphenylaluminum **2** as a model. Initially we have observed that the formation of desired product in less yield when triphenylaluminum(1 mmol) reacted with free isatin(1 mmol) in toluene at rt. Next we focused to examine the reaction in detail to increase the reaction rate and yield. Surprisingly, the extreme increase in the reaction rate and yield (90%) of **3a** was observed when the temperature raised to 70 °C without using any catalyst. And we also observed that there is no change in yield even if the temperature is raised to 100 °C. The reaction completed smoothly within 3 h at 70 °C to give 3-hydroxy-3-(phenyl)indolin-2-one **3a** which was confirmed by analyzing spectral data (Table 2, entry 1). Though the reaction proceeds with 1:1 ratio of reactant, the best results were obtained by 2 equiv ratio of $AlPh_3$.

Encouraged by these results, next we have studied the model reaction in different solvents such as DMSO, toluene, xylene, dioxane, acetonitrile, THF, and DCM. We have noticed that the reaction proceeded in all the solvents with a different degree of conversion (Table 1). However, toluene was the solvent of choice in terms of reaction time and yield.

The scope of this catalyst-free protocol was investigated under optimal condition[17] and the results are summarized in Table 2. Isatins bearing different substituents on the nitrogen atom and/

Table 2
3-Hydroxy-3-(alkyl/aryl)-indolin-2-one derivatives formation by using organoaluminum

Entry	Isatin	Al (Alky/Aryl)$_3$	Product[a]	Time (h)	Yield[b](%)
1		$AlPh_3$	 **3a**	3	90
2		$AlPh_3$	 **3b**	3	93
3		$AlPh_3$	 **3c**	3	92
4		$AlPh_3$	 **3d**	3	93
5		$AlPh_3$	 **3e**	3	95
6		$AlPh_3$	 **3f**	3	94
7		$AlPh_3$	 **3g**	3.5	80
8		$AlEt_3$	 **3h**	3.5	85
9		$AlEt_3$	 **3i**	3.5	84
10		$AlEt_3$	 **3j**	3.5	75
11		$AlEt_3$	 **3k**	3.5	80

(*continued on next page*)