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Mild and efficient synthesis of isoindigo derivatives catalyzed by Lewis acid

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ABSTRACT

A mild and efficient $ZrCl_4$-catalyzed synthesis of isoindigo derivatives from isatins and indolin-2-ones in refluxing ethanol is described. A variety of new functionalized isoindigo derivatives are obtained by simple filtration. Lewis acid was first used as catalyst in the synthesis of isoindigo derivatives.

1. Introduction

Isoindigo, as a structural isomer of the famous indigo pigment is an important bis-indole heterocyclic molecule, which has attracted much attention in drug development.[1] For example, meisoindigo has been employed for the treatment of chronic myeloid leukemia in China[2] and Natura is proved to be an excellent inhibitor for cyclin-dependent kinases (CDKs) (Fig. 1).[3] Moreover, isoindigo is becoming a popular electron acceptor unit for organic electronic materials[4,5] and can be used as the key intermediate for the synthesis of natural products.[6]

The most commonly used approach to structural diverse isoindigo derivatives is based on the condensation of isatins and indolin-2-ones in refluxing acetic acid in the presence of concentrated hydrochloric acid[7] or *p*-toluene sulphonic acid system.[8,9] In recent years, a large number of isoindigo-based functionalized polymers and drug candidates have been prepared by this route. In addition, many symmetrically substituted isoindigos can be synthesized by the homocoupling of isatins[10] or indolin-2-ones.[11] Apparently, the substrate scope is often limited by the strong acid reaction media and high reaction temperature (above 120 ^{o}C). More notably, the work-up procedure is a little tedious and purification by column chromatography is required in some cases.[1b,1c,12] Accordingly, new approach to isoindigo derivatives with wide substrate scope, easy work-up procedure as well as enhanced reaction efficiency is still highly desirable. Zirconium (IV) tetrachloride ($ZrCl_4$) as a green Lewis acid is widely employed in organic synthetic chemistry due to the low toxicity, moisture stability, low cost and excellent efficiency.[13] In a continuation of our effort to obtain valuable heterocycles from isatins,[14] we herein would like to report a $ZrCl_4$-catalyzed efficient synthesis of isoindigos from isatins and indolin-2-ones in refluxing ethanol.

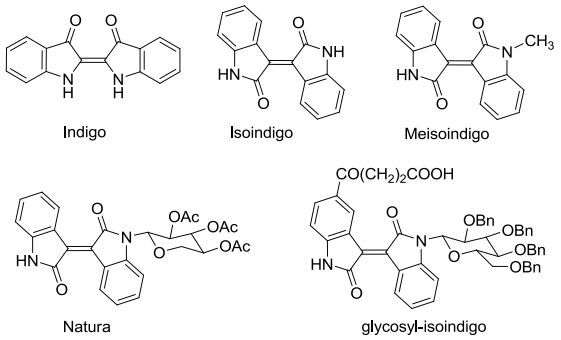

Figure 1 Structures of indigo and isoindigo derivatives.

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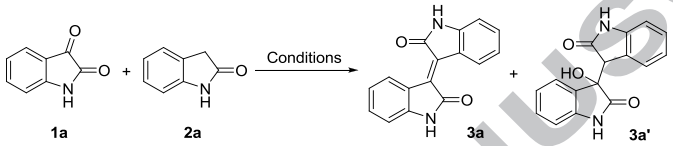
2. Results and discussion

Initially, isatin (**1a**, 1.0 mmol) and indolin-2-one (**2a**, 1.0 mmol) were stirred in refluxing ethanol in the presence of a catalytic amount of iodine (0.2 mmol), and a red solid precipitated. The structure was confirmed as isoindigo (**3a**) with 73% isolated yield. Meanwhile, a trace amount of undehydrated product 3-hydroxy-3,3'-biindoline-2,2'-dione (**3a'**) was also observed (Table 1, entry 1). Next, the reaction conditions were further optimized by screening various catalysts, solvents and temperature. When the commonly used *L*-Proline, $ZnCl_2$ and AcOH were examined, the reactions gave **3a'** as the main product (entries 2–4). In the absence of any catalyst, only **3a'** was obtained in excellent yield (entry 5).[15] Satisfyingly, $InCl_3$ and $ZrCl_4$ were efficient catalysts for the formation of **3a**, and the latter gave a slightly higher yield (entries 6, 7). Reducing the loading of $ZrCl_4$ did not significantly decrease the yield (entries 8, 9). Decreasing the reaction temperature to 40 ^oC resulted in **3a** in 60% yield (entry 10). MeCN was also an efficient solvent, but the reaction gave a lower yield in MeOH and THF (entries 11–13). Finally, the optimized reaction conditions were identified as the reaction of **1a** with 1.0 equivalent of **2a** in refluxing ethanol in the presence of 10 mol% $ZrCl_4$.

Table 1
Optimization of reaction conditions for the synthesis of **3a**[a]



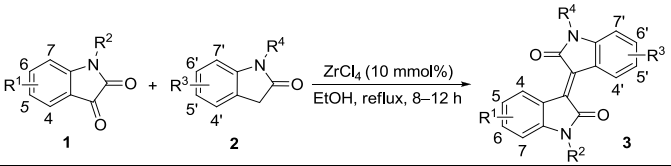
Entry	Catalyst (equiv)	Solvent (mL)	Temp. (^oC)	Yield[b] (%, **3a**/**3a'**)
1	I_2 (0.2)	EtOH	reflux	73/trace
2	*L*-Proline (0.2)	EtOH	reflux	trace/96
3	$ZnCl_2$ (0.2)	EtOH	reflux	20/76
4[c]	AcOH	EtOH	reflux	21/70
5	None	EtOH	reflux	0/96
6	$InCl_3$ (0.2)	EtOH	reflux	88/trace
7	$ZrCl_4$ (0.2)	EtOH	reflux	92/trace
8	$ZrCl_4$ (0.1)	EtOH	reflux	91/trace
9	$ZrCl_4$ (0.05)	EtOH	reflux	89/trace
10	$ZrCl_4$ (0.1)	EtOH	40	60/30
11	$ZrCl_4$ (0.1)	MeCN	reflux	90/trace
12	$ZrCl_4$ (0.1)	MeOH	reflux	74/<5
13	$ZrCl_4$ (0.1)	THF	reflux	10/32

[a] All the reactions were carried out using isatin (**1a**, 1.0 mmol) and indolin-2-one (**2a**, 1.0 mmol) in solvent (5 mL) for 9 h, unless otherwise specified.
[b] Isolated yield.
[c] 0.5 mL AcOH was used.

With the optimized reaction condition in hand (Table 1, entry 8), the reactions of a variety of substituted isatins with indolin-2-one (**2a**) were examined, and the results were summarized in Table 2. Methoxy and halogenated (-F, -Cl, -Br) substituted isatins gave the corresponding products **3b–e** in 85–94% yields (Table 2, entries 2–5). Notably, drug meisoindigo (**3f**) was obtained in 86% yield (Table 2, entry 6). Other *N*-alkyl (-$CH_2C_6H_5$, -CH_2COOEt) substituted isatins also delivered **3g** and **3h** in good yields (Table 2, entries 7, 8). However, *N*-acetyl substituted isatin resulted in the deacetylated product isoindigo (**3a**) as the main product in 69% yield (Table 2, entry 9). The halogenated molecules were easily converted into other valuable derivatives via classic C-C/C-N coupling reactions, then 5'-/6'-chloro- and 5'-bromo-substituted indolin-2-ones were smoothly reacted with isatins to give the corresponding products **3d**, **3i–o** and **3e** 81–95% yields (Table 2, entries 10–18). To our delight, *N*-phenyl substituted indolin-2-one was also a suitable substrate for this type of reaction, furnishing the substituted isoindigos **3p–w** in 83–91% yields (Table 2, entries 19–26).

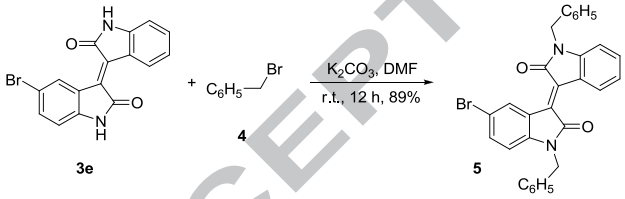
We further explored the *N*-alkylation reaction of *N*-unsubstituted isoindigo using 5-bromo-3,3'-biindolinylidene-2,2'-dione (**3e**) as a representative example. The mixture of **3e** and benzyl bromide (**4**) was stirred in DMF in the presence of K_2CO_3 at room temperature for 12 h, and the reaction gave the expected bis-*N*-alkylated product **5** in 89% isolated yield (Scheme 1).

Table 2
The scope of substrates[a]



Entry	R^1	R^2	R^3	R^4	Product	Yield[b] (%)
1	H	H	H	H	**3a**	91
2	5-OMe	H	H	H	**3b**	85
3	7-F	H	H	H	**3c**	94
4	5-Cl	H	H	H	**3d**	86
5	5-Br	H	H	H	**3e**	87
6	H	Me	H	H	**3f**	86
7	H	$CH_2C_6H_5$	H	H	**3g**	86
8	H	CH_2COOEt	H	H	**3h**	84
9	H	COMe	H	H	**3a**	69
10	H	H	5'-Cl	H	**3d**	95
11	5-OMe	H	5'-Cl	H	**3i**	82
12	5-Cl	H	5'-Cl	H	**3j**	88
13	5-Br	H	5'-Cl	H	**3k**	92
14	H	Me	5'-Cl	H	**3l**	94
15	H	H	6'-Cl	H	**3m**	81
16	5-Cl	H	6'-Cl	H	**3n**	86
17	7-F	H	6'-Cl	H	**3o**	83
18	H	H	5'-Br	H	**3e**	95
19	H	H	H	C_6H_5	**3p**	91
20	H	Me	H	C_6H_5	**3q**	85
21	H	*i*-Pr	H	C_6H_5	**3r**	91
22	H	$CH_2C_6H_5$	H	C_6H_5	**3s**	85
23	H	CH_2COOEt	H	C_6H_5	**3t**	88
24	5-Br	$CH_2C_6H_5$	H	C_6H_5	**3u**	83
25	5-Br	*n*-Bu	H	C_6H_5	**3v**	87
26	5-Br	3-Octyl	H	C_6H_5	**3w**	86

[a] All of the reactions were carried out with **1** (1.0 mmol), **2** (1.0 mmol), $ZrCl_4$ (0.01 mmol) in anhydrous EtOH (5 mL) under reflux for 8–12 h, unless otherwise specified.
[b] Isolated yields.



Scheme 1. *N*-alkylation reaction of **3e**

In summary, we have developed a $ZrCl_4$-catalyzed efficient synthesis of isoindigo derivatives from isatins and indolin-2-ones in refluxing ethanol. Lewis acid was used as catalyst in the synthesis of isoindigo derivatives for the first time. This method has the advantages of mild reaction conditions, highly reaction efficiency, functional group tolerance and easy work-up procedure. A number of new functionalized isoindigos are obtained by simple filtration. All these unknown compounds were characterized by means of ^1H NMR, ^{13}C NMR, HRMS and IR spectra. Further investigations on the applications of isoindigos to other valuable nitrogen-containing heterocycles[16] are currently underway in our laboratory.

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Supplementary data

Supplementary data related to this article can be found, in the online version at:

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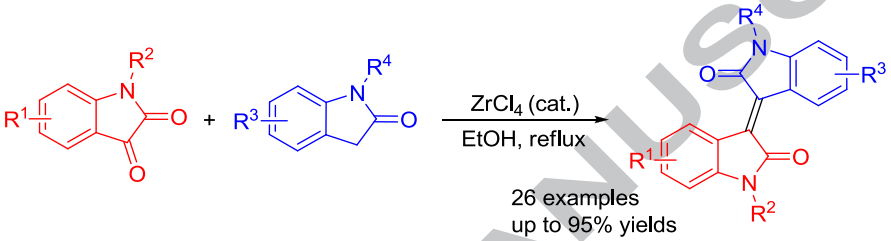

Research highlights

- This method allows the facile approach to new functionalized isoindigos under mild conditions.
- The products can be obtained only by simple filtration.
- Lewis acid is used as catalyst in the synthesis of isoindigo derivatives for the first time.