ACS Catalysis

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Highly Efficient Assembly of 3-Hydroxy Oxindole Scaffold via a Catalytic Decarboxylative [1,2]-Addition Strategy

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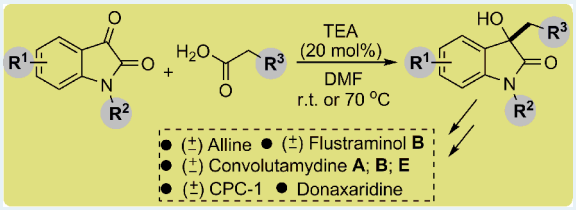
Supporting Information

ABSTRACT: The 3-hydroxy-2-oxindole scaffold is being continuously discovered to be at the core of a diverse set of natural products. Herein, we document a highly efficient catalytic decarboxylative [1,2]-addition strategy to quickly assemble this scaffold, using a catalytic amount of weak base.



KEYWORDS: *decarboxylation, 1,2-addition, organocatalysis, oxindole*

Over the past few decades, natural products have proven to be useful small molecule probes in the medicinal community.[1,2] Since they have coevolved with their putative biological targets, natural products intersect biological space effectively and perturb its function in a highly controlled manner. It is not surprising that natural products have endured as promising leads for drug discovery. A rapid access to small molecules that are guided by natural products appears to be quintessential for the success of a chemical genetics/genomics-based program. The design and synthesis of novel scaffolds as chiral core structures for the library generation of natural product-like derivatives is an essential step in accessing a wide range of structural complexes in an efficient manner.[3−7]

Herein, we disclose a concise decarboxylative[8−11] [1,2]-addition process of readily accessible α-functionalized carboxylic acids with isatins under mild reaction conditions to assemble the valuable 3-functionalized 3-hydroxy-2-oxindoles (Figure 1).[12,13]

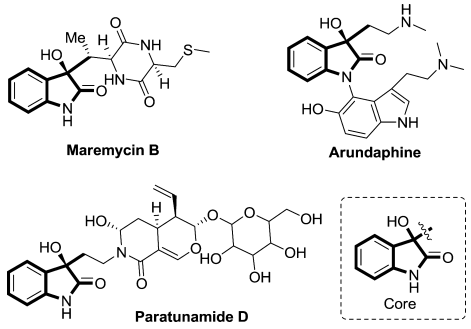
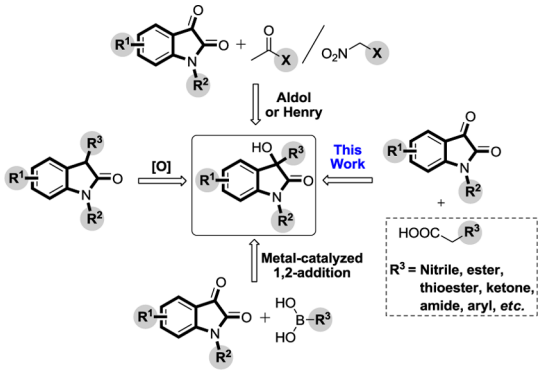


Figure 1. Representative bioactive natural products built on a 3-hydroxy-2-oxindole core scaffold.

Good to excellent yields have been obtained at a suitable condition. These features render this synthetic protocol particularly attractive for practical application in drug discovery. It is noteworthy that the synthetic value has been broadly demonstrated in the formal and total synthesis of bioactive natural products,[12−21] such as (±)-flustraminol B, (±)-convolutamydine A,(±)-alline, donaxaridine, (±)-convolutamydine E, (±)-convolutamydine B, and (±)-CPC-1. Some elegant works have been reported to directly construct the 3-functionalized-3-hydroxy-2-oxindole framework (Scheme 1).

Scheme 1. Routes for the Preparation of 3-Functionalized 3-Hydroxy-2-oxindole Framework



One of the most straightforward strategies is the catalytic aldol reactions of ketones and aldehydes with isatins.[22−24] In line with the nucleophilic addition to the 3-carbonyl of isatins as a strategy for the synthesis of 3-substituted-3-hydroxy oxindoles, metal-mediated additions of carbon nucleophiles/equivalents, such as boronic acids, have been explored.[25−27]

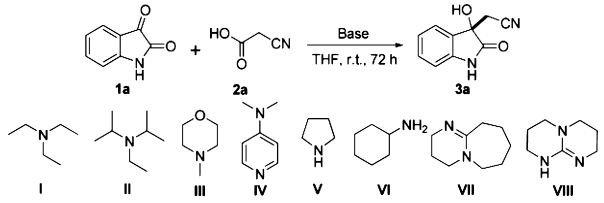
Received: September 23, 2012
Revised: October 27, 2012
Published: October 31, 2012

   dx.doi.org/10.1021/cs300628w | ACS Catal. 2012, 2, 2622−2625

Recently, a catalytic Henry reaction of isatins with alkanes has also been reported to make this core structure.[28] In addition, the oxidation of 3-substituted oxindoles is showing itself to be a useful method for the construction of this medicinal scaffold.[29−31] Notably, a dimeric quinidine-catalyzed enantioselective amino-oxygenation of oxindoles has been reported to generate chiral 3-substituted oxindoles.[32] However, all the above methods are limited to special substrates.[33−37] To our knowledge, there has been no powerful method that can construct a 3-hydroxy oxindole scaffold and bear a wide spectrum of functional groups at the C3 position (Scheme 1). As part of a program geared toward the design and development of novel organocatalytic strategy for the efficient and mild synthesis of 3-functionalized-3-hydroxy-2-oxindole framework, we proposed a decarboxylative [1,2]-addition of various α-functionalized acetic acids to isatins catalyzed by a weak base.

We began our investigation by examining the base-promoted reaction of isatin **1a** and cyanoacetic acid **2a** (Table 1). The

Table 1. Base Effect[a]



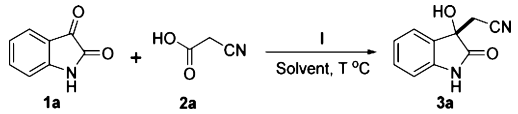
entry	base	yield (%)[a]	entry	base	yield (%)[b]
1	**I**	82	7	**VII**	80
2	**II**	69	8	**VIII**	43
3	**III**	18	9	Li_2CO_3	<5
4	**IV**	48	10	Cs_2CO_3	<5
5	**V**	42	11	NaOAc	27[d]
6	**VI**	*c*	12	NaOH	48

[a]Reaction conditions: THF (1.0 mL), **1a** (0.2 mmol, l.0 equiv), **2a** (0.4 mmol, 2.0 equiv), base (1.0 equiv), 72 h, room temperature. [b]Yield of isolated product after column chromatography. [c]No reaction. [d]NaOAc was dissolved in H_2O (0.1 mL), 72 h.

initial experimental results showed that the use of a stoichiometric amount of triethylamine **I** (1.0 equiv) enabled a reaction between isatin **1a** and cyanoacetic acid **2a** to afford an 82% yield at room temperature (Table 1, entry 1, 72 h). To seek a more efficient catalyst, we then examined some other tertiary amines, such as second and primary amines, but the reaction yields were lower (Table 1, entries 2−6, <69%). Surprisingly, super organic bases, **VII** and **VIII**, did not show a higher activity, as expected (entries 7 and 8). In addition, several inorganic bases were also investigated, but the results demonstrated these inorganic bases are not efficient promoters in this reaction.

Having this finding in hands, we started to probe other parameters. A high yield was obtained if the reaction was carried out in polar solvent DMF (Table 2, entry 10, 90%, 72 h, room temperature). Other polar solvents, such as water and isopropyl alcohol, however, proved to be poor media in this reaction (Table 2, entries 8 and 9, no reaction and 49%, respectively). To reduce the reaction time, we tried to increase the reaction temperature. The results showed that a higher reaction temperature can largely improve the reaction rate (entry 12, 70 °C, 95%, 1 h). As shown in Table 2, a 20 mol % catalyst **I** also efficiently promoted the reaction (entry 13, 95%, 3 h). However, a high reaction

Table 2. Optimization of Other Parameters[a]



entry	solvent	*t* (h)	*I* (mol %)	*T* (°C)	yield (%)[b]
1	CH_2C1_2	72	100	r.t.	38
2	toluene	72	100	r.t.	*f*
3	THF	72	100	r.t.	82
4	Et_2O	72	100	r.t.	*f*
5	MeCN	72	100	r.t.	72
6	acetone	72	100	r.t.	65
7	EtOAc	72	100	r.t.	33
8	H_2O	72	100	r.t.	*f*
9	IPA[e]	72	100	r.t.	49
10	DMF	72	100	r.t.	90
11	DMF	18	100	50	98
12	DMF	1	100	70	95
13[c]	**DMF**	**3**	**20**	**70**	**95**
14[d]	DMF	3	20	70	75
15	DMF	6	10	70	88
16	DMF	8	5	70	81

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), concentration (0.2 mol/L). [b]Yield of isolated product after column chromatography. [c]**2a** (0.22 mmol, 1.1 equiv). [d]Concentration (1.0 mol/L). [e]Isopropyl alcohol. [f]No reaction.

concentration (1.0 mol/L) caused a loss of reaction yield because of some unknown side reactions (entry 14, 75%). In addition, the low catalyst loading also supported a good reaction yield in a suitable time (entry 16, 5 mol % **I**, 81%, 8 h).

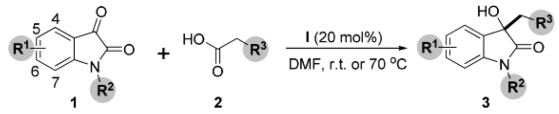
Having established a standard reaction protocol, we then probed a diverse set of isatins **1** and α-functionalized acetic acids **2**. As revealed in Table 3, the process proves to be a general strategy to construct 3-functionalized 3-hydroxyoxindoles **3**. Impressively, all reactions proceeded quickly (3−24 h), in good to excellent yields (up to 96%). The substitution pattern of R^1 was observed to possess limited effect on reaction rate, regardless of the natural, electron-donating, or electron-withdrawing properties ofthe substituents (Table 1, entries 1−16). We also found that the introduction of R^2 did not obviously affect this reaction (entries 17−20, 80−95%, 3 h). More importantly, a variety of α-functionalized groups, such as nitrile, esters, thioester, amide, ketone, and aryl groups, were successfully introduced to the core scaffold, and desired products **3u−3z** were achieved in moderate to high yields (entries 21−26, 61−95%, 3−24 h).

To illustrate the broad synthetic utility of this methodology, we undertook the formal synthesis of several natural products, such as (±)-flustraminol B (eq 1), (±)-convolutamydine A (eq 2), (±)-alline (eq 3), donaxaridine (eq 5), (±)-convolutamydine E (eq 4), and (±)-convolutamydine B (eq 4). As shown in eqs 1−5, we efficiently synthesized a series of important intermediates—**3a**, **3m**, **3w** and **7**—which could be efficiently converted to targeted natural products (±)-alline, **6**; (±)-flustraminol B, **4**; donaxaridine, **11**; and (±)-convolutamydine E, **8**; and (±)-convolutamydine B, **9**; via known methods, respectively. Moreover, (±)-convolutamydine A, **5**, was directly synthesized by our one-pot decarboxylative [1,2]-addition strategy in 88% yield.

In addition, this method was applied to efficiently synthesize (±)-CPC-1. The synthesis commenced with an initial step, the bis-methylation of **3a**, to afford the N,O-dimethylated intermediate, which was then converted to the Boc-protected

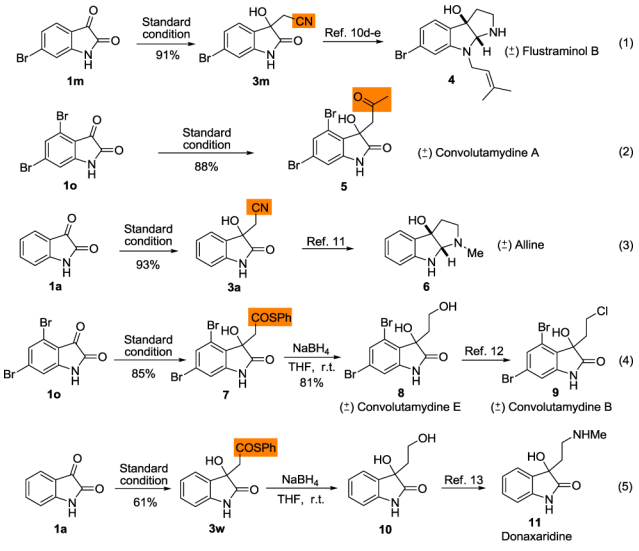
dx.doi.org/10.1021/cs300628w | ACS Catal. 2012, 2, 2622−2625

Table 3. Substrate Scope[a]



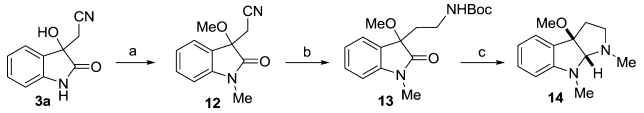
entry	R^1	R^2	R^3	T (h)	yield (%)[b]
1	H	H	CN (**3a**)	3	95
2	5-F	H	CN (**3b**)	3	95
3	5-C1	H	CN(**3c**)	3	96
4	5-Br	H	CN(**3d**)	3	92
5	5-NO_2	H	CN (**3e**)	3	85
6	5-MeO	H	CN (**3f**)	3	91
7	5-Me	H	CN(**3g**)	3	92
8	5-*i*-Pr	H	CN(**3h**)	3	88
9	5-*n*-C_7H_{15}	H	CN(**3i**)	6	73
10	4-C1	H	CN (**3j**)	3	96
11	4-Br	H	CN (**3k**)	3	90
12	6-Cl	H	CN (**3l**)	3	93
13	6-Br	H	CN (**3m**)	3	91
14[c]	4,6-Me_2	H	CN (**3n**)	24	90
15	4,6-Br_2	H	CN (**3o**)	3	87
16	5,7-Br_2	H	CN(**3p**)	3	85
17	H	Bz	CN (**3q**)	3	81
18	H	Ac	CN (**3r**)	3	80
19	H	Bn	CN (**3s**)	3	95
20	H	Me	CN (**3t**)	3	91
21	H	H	CO_2Me (**3u**)	3	90
22[d]	H	H	CO_2Ph (**3v**)	24	92
23[d]	H	H	COSPh (**3w**)	24	61
24	H	H	CONHPh (**3x**)	18	81
25	H	H	COPh (**3y**)	3	86
26	H	H	4-NO_2Ph (**3z**)	3	95

[a]Reaction conditions: DMF (1.0 mL), **1** (0.2 mmol, 1.0 equiv), **2** (0.22 mmol, 1.1 equiv), **I** (20 mol %), 70 °C. [b]Yield of isolated product after column chromatography. [c]**I** (1.0 equiv). [d]Room temperature.

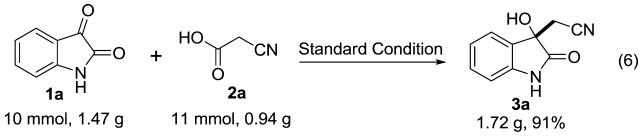


amine in the presence of $NiCl_2$ and reducing agent $NaBH_4$. Followed that, the Boc protecting group was transferred into a methyl group by using Red-Al, and then the intermediate was cyclized with the oxindole functionality to afford the desired alkaloid (±)-CPC-1 (Scheme 2). Meanwhile, the large-scale

Scheme 2. Synthesis of (±)-CPC-1[a]



[a]**14**Reagents: (a) Cs_2CO_3, Me_2SO_4, CH_3CN/DMF, 71%; (b) $NiCl_2$/$NaBH_4$, $(Boc)_2O$, MeOH, r.t., 77%; (c) Red-Al, toluene, 0−80 °C.



synthesis by using 1.47 g of **1a** to react with 0.94 g of **2a** demonstrated that the process is practicable (eq 6, 91%).

In conclusion, inspired by the "medicinal" scaffold of 3-functionalized 3-hydroxyoxindoles, we have documented a concise decarboxylative [1,2]-addition strategy based on readily available isatins and α-functionalized acetic acids. We have demonstrated the broad synthetic utility of our catalytic protocol in the efficient assembly of pharmaceutical important 3-hydroxyoxindole natural products. Further applications of this catalytic strategy are underway.

EXPERIMENTAL SECTION

General Procedure: To a solution of isatin **1a** (29.4 mg, 0.20 mmol) in 1.0 mL DMF was added cyanoacetic acid **2a** (18.7 mg, 0.22 mmol) at room temperature, followed by adding catalyst **I** TEA (5.6 μL, 0.04 mmol). The mixture was stirred at 70 °C for 3 h. The crude product was purified by column chromatography on silica gel and eluted by hexane/EtOAc = 2:1 to afford 35.8 mg (95% yield) of the desired product **3a** as a white solid.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectroscopic and analytic data of the compounds 1 and 3 are included. This material is available free of charge via the Internet at http://pubs.acs.org.)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is supported by the National University of Singapore under MOE AcRF FRC Grants R-143-000-480-112, R-143-000-443-112 and NRF-CRP7-2010-03

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dx.doi.org/10.1021/cs300628w | *ACS Catal.* 2012, 2, 2622−2625