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Synthesis of 6-Substituted 6*H*-Indolo[2,3-*b*]quinolines from Isoindigos

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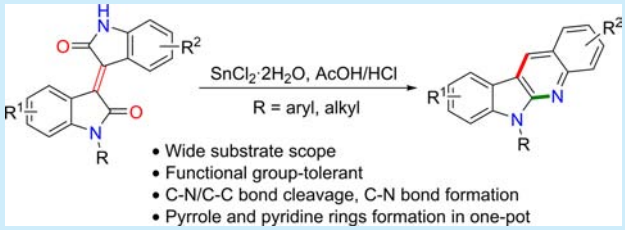
Supporting Information

ABSTRACT: A facile approach to 6-aryl/alkyl substituted 6*H*-indolo[2,3-*b*]quinolines from mono-*N*-substituted isoindigo derivatives in the presence of $SnCl_2 \cdot 2H_2O$ in acid media is described. Pyrrole and pyridine rings are synchronously constructed in one pot for these tetracyclic molecules. A plausible reduction/hydrolysis/decarboxylation/cyclization/aromatization domino reaction mechanism is proposed. Bis-*N*-substituted isoindigo only gives the corresponding reduction product, 3,3′-bioxindole.



The root of the West African plant *Cryptolepis Sanguinolenta* has long been used as traditional medicine for the treatment of a variety of diseases, such as malaria, amebiasis, and rheumatism.[1] Indoloquinoline alkaloids represent a new class of drug leads,[2] and a dozen or so indoloquinolines, including cryptolepine (**I**), 11-isopropylcryptolepine (**II**), isocryptolepine (**III**), isoneocryptolepine (**IV**), neocryptolepine (**V**), and 11-methylneocryptolepine (**VI**), are isolated from this plant (Figure 1).[3] Among them, neocryptolepine (5-methyl-5*H*-

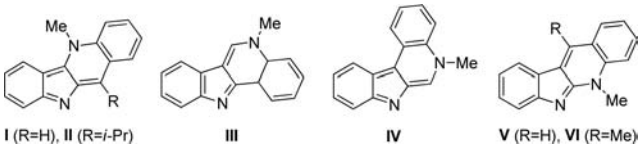
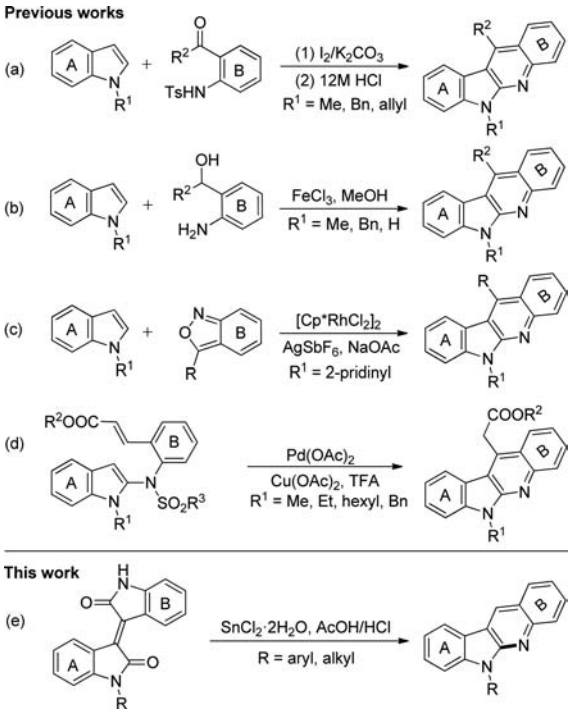


Figure 1. Naturally occurring indoloquinoline alkaloids.

indolo[2,3-*b*]quinoline) and its derivatives display strong antiplasmodial, antimicrobial, and cytotoxic activities.[4] Several routes have been reported for the total synthesis of this natural molecule, most of which involve methylation of its precursor 6*H*-indolo[2,3-*b*]quinoline.[5] In recent years, in order to expand the molecular library of this tetracyclic framework for the discovery of pharmaceutically active compounds, many excellent approaches to 6*H*-indolo[2,3-*b*]quinolines have been developed.[6−9] However, only a few routes have focused on the preparation of 6-substituted 6*H*-indolo[2,3-*b*]quinolines.[10,11] For example, Liang described an iodine-mediated one-pot access to 6-alkyl substituted 6*H*-indolo[2,3-*b*]quinolines by an electrophile-triggered cross-amination/Friedel−Crafts alkylation of indole with 1-(2-tosylaminophenyl)ketone (Scheme 1, path a).[12] Wang reported an efficient iron-promoted synthesis of 6*H*-indolo[2,3-*b*]quinolines by the reactions of aminophenyl alcohols and indoles (Scheme 1, path b).[13] Wang and Li illustrated a fascinating Rh(III)-catalyzed synthetic method for 6-(2-pyridinyl/2-pyrimidinyl)-6*H*-indolo[2,3-*b*]quinolines from

Scheme 1. Pathways for the Synthesis of 6-Substituted 6*H*-Indolo[2,3-*b*]quinolines



indoles and isoxazoles. Notably, the 2-pyridinyl or 2-pyrimidinyl group as a directing group is required and crucial for this transformation (Scheme 1, path c).[14] Pal and co-workers found that 11-carboxymethyl substituted 6*H*-indolo[2,3-*b*]quinolines could be obtained by a one-pot Pd(II)-catalyzed intramolecular

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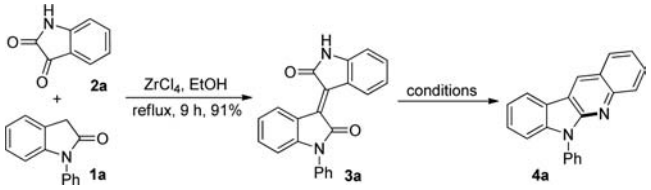
oxidative C3−H alkenylation of the indole ring of (*E*)-alkyl-3-(2-(1*H*-indol-2-ylamino)phenyl)acrylate derivatives followed by desulfonylation (Scheme 1, path d).[15] Apparently, most of these excellent methods experience difficulty in accessing 6-aryl substituted 6*H*-indolo[2,3-*b*]quinolines, probably due to inaccessible starting materials or limited substrate scope. Sometimes the use of expensive metal catalysts is required. Accordingly, a novel synthetic approach to 6-substituted, especially 6-aryl substituted 6*H*-indolo[2,3-*b*]quinolones, is still highly desired. Recently, we have developed a simple and mild method for the synthesis of isoindigos from easily available indolin-2-ones and isatins catalyzed by the Lewis acid $ZrCl_4$.[16] Herein, we report an efficient synthesis of 6-aryl/alkyl substituted 6*H*-indolo[2,3-*b*]quinolines from isoindigo derivatives in the presence of $SnCl_2{\cdot}2H_2O$ in acid media (Scheme 1, path e).

It is well-known that unsaturated 1,4-diketones are important precursors for the Paal−Knorr cyclization reaction.[17] Isoindigo can also be regarded as an unsaturated 1,4-diketone derivative and is widely used in organic synthesis.[18] In our initial study, we expected to synthesize these novel fused-ring heterocycles from (*E*)-1-phenyl-[3,3′-biindolinylidene]-2,2′-dione (**3a**), which was obtained by the condensation of 1-phenylindolin-2-one (**1a**) and isatin (**2a**).[16a] Heating **3a** in an acetic acid and concentrated hydrochloric acid solution (v/v, 1:2) at reflux for 12 h using commonly used zinc dust as the reductant led to an unexpected conjugated tetracyclic product 6-phenyl-6*H*-indolo[2,3-*b*]quinoline (**4a**) in 45% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions for the Synthesis of 4a[a]



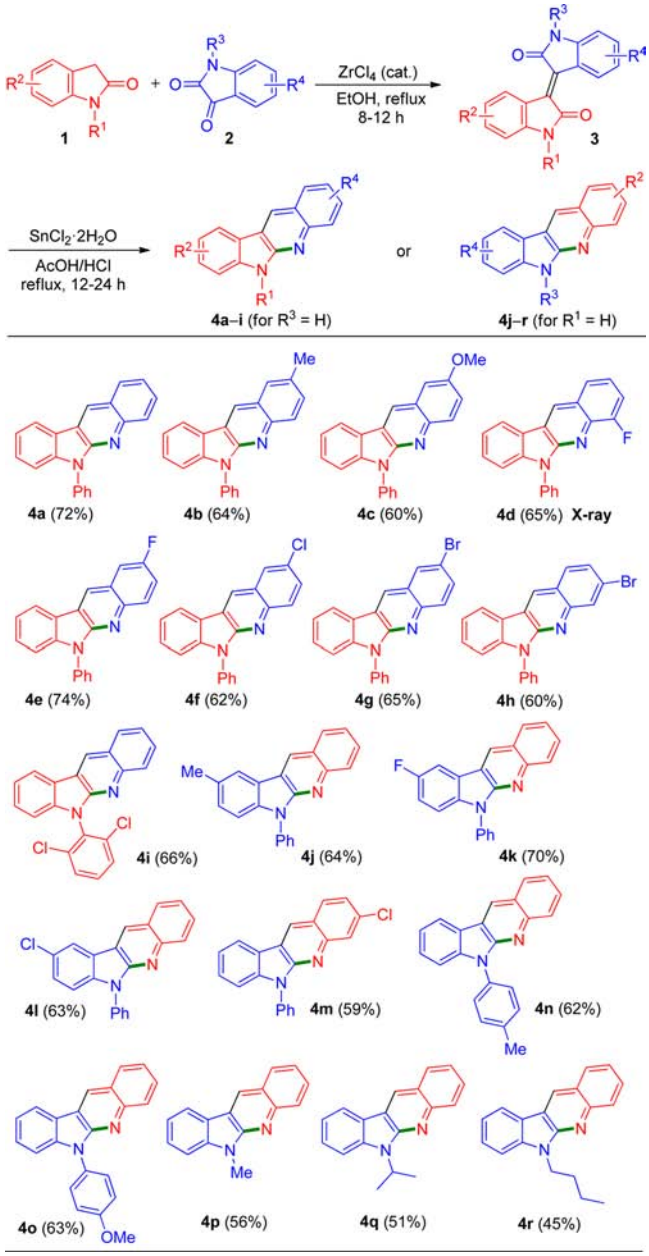
entry	reductant (equiv)	AcOH/HCl (v/v)	temp (°C)	time (h)	yield[b] (%)
1	Zn (10)	1:2	120	12	45
2	Fe (10)	1:2	120	12	<5
3	$SnCl_2{\cdot}2H_2O$ (10)	1:2	120	12	65
4	$SnCl_2{\cdot}2H_2O$ (10)	1:2	120	24	67
5	$SnCl_2{\cdot}2H_2O$ (10)	1:2	120	24	72[c]
6	$SnCl_2{\cdot}2H_2O$ (10)	1:1	120	24	50
7	$SnCl_2{\cdot}2H_2O$ (10)	1:4	120	24	55
8	$SnCl_2{\cdot}2H_2O$ (5)	1:2	120	24	46
9	$SnCl_2{\cdot}2H_2O$ (2)	1:2	120	24	20
10	$SnCl_2{\cdot}2H_2O$ (10)	1:2	100	24	58
11	$SnCl_2{\cdot}2H_2O$ (10)	1:2	80	24	49
12	$SnCl_2{\cdot}2H_2O$ (10)	1:2	25	24	0

[a]Unless otherwise specified, all of the reactions were carried out using **3a** (0.2 mmol) in acetic acid and concentrated hydrochloric acid (3 mL). [b]Isolated yield. [c]Concentrated hydrochloric acid was added three times, and the acid volume/drop time/duration time were 1.0 mL/0 h/5 min, 0.5 mL/3 h/5 min, and 0.5 mL/6 h/5 min, respectively.

Iron powder was less active for this transformation (entry 2).[19] To our delight, the yield of **4a** could be increased to 65% when $SnCl_2{\cdot}2H_2O$ was employed (entry 3).[20] Prolonging the reaction time to 24 h led to a slight improvement in the yield (entry 4). The reaction gave the best result when concentrated hydrochloric acid was added three times in order to reduce volatilization (entry 5). Varying the ratio of acid or reducing the amount of reductant resulted in a lower yield (entries 6−9). In addition, the reaction temperature influenced the yield and no expected product was obtained at room temperature (entries 10−12).

With the aforementioned optimized reaction conditions in hand (Table 1, entry 5), the substrate scope of isoindigos (**3**), which was synthesized from isatins (**1**) and indolin-2-ones (**2**) (see Supporting Information), was explored, and the results are summarized in Scheme 2. 1-Phenylindolin-2-one (**1a**) reacted

Scheme 2. Substrate Scope of Isoindigos[a,b]



[a]Unless otherwise specified, all of the reactions were carried out using **3** (0.2 mmol) and $SnCl_2{\cdot}2H_2O$ (2.0 mmol) in acetic acid and concentrated hydrochloric acid (3 mL; v/v = 1/2). Concentrated hydrochloric acid was added three times, and the acid volume/drop time/duration time were 1.0 mL/0 h/5 min, 0.5 mL/3 h/5 min, and 0.5 mL/6 h/5 min, respectively. [b]Isolated yield.

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smoothly with isatins bearing electron-donating (−Me, −OMe) or halogen substituted groups (−F, −Cl, −Br) on the phenyl ring, leading to isoindigos **3b−h** (R^3 = H) in excellent yields, which were converted into the corresponding 6-phenyl-substituted 6*H*-indolo[2,3-*b*]quinolines **4b−h** in 60−74% yields. The structure of **4d** was confirmed by X-ray single-crystal diffraction analysis (Figure 2). In addition, 6-(2,6-dichloro-

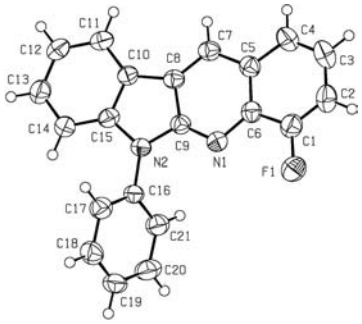
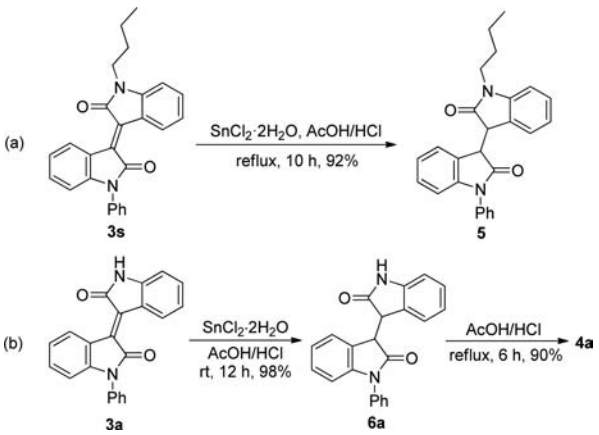


Figure 2. X-ray structure of compound **4d**.

phenyl)-6*H*-indolo[2,3-*b*]quinoline **4i** was also obtained in 66% yield from **3i**. Encouraged by the results achieved above, the substrate scope was further expanded to substituted isoindigos **3j−r** (R^1 = H). It was found that 6-aryl substituted 6*H*-indolo[2,3-*b*]quinolines **4j−o** could be obtained in good yields (59−70%). Satisfyingly, mono-*N*-alkyl (−Me, −*i*-Pr, −*n*-Bu) substituted isoindigos **3p−r** were also suitable for this reaction, furnishing the corresponding 6-*N*-alkyl substituted 6*H*-indolo[2,3-*b*]quinolines **4p−r** in moderate yields.

Next, bis-*N*-substituted isoindigo **3s** was prepared from 1-phenylindolin-2-one and 1-butylindoline-2,3-dione (see Supporting Information). The reaction only gave the reduction product 3,3′-bioxindole **5** in 92% isolated yield under the above-mentioned standard reaction conditions (Scheme 3a), as a

Scheme 3. Control Experiments



mixture of two epimers in 1:2 (*syn*/*anti*) ratio according to ^{1}H NMR spectroscopy.[21] The single *syn* isomer was obtained by crystallization of the mixture from anhydrous ethanol and was identified by X-ray single-crystal diffraction analysis (Figure 3).

Moreover, in order to clarify the reaction mechanism, the saturated 1,4-dicarbonyl compound **6a** was easily isolated from **3a** in the presence of $SnCl_2·2H_2O$ under the acid conditions at room temperature, which could be converted into target

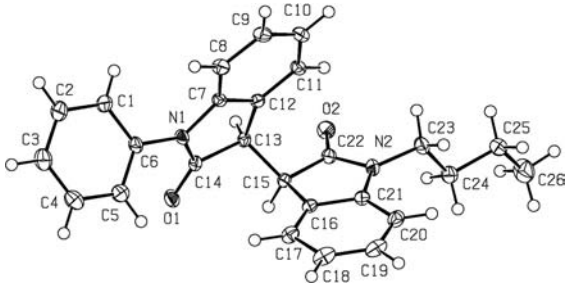
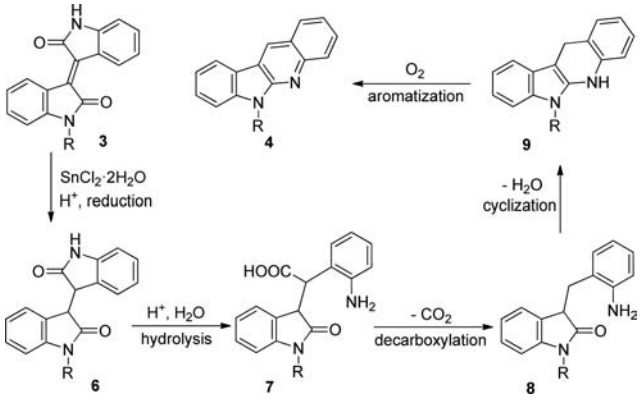


Figure 3. X-ray structure of compound **5**.

molecule **4a** in excellent yield in acetic acid and concentrated hydrochloric acid system at reflux (Scheme 3b).

On the basis of these experimental results and previous literature, it was clear that the *N*-unsubstituted amide bond could hydrolyze in the acid medium of this reaction. Therefore, a possible reaction mechanism is presented, as shown in Scheme 4.

Scheme 4. Possible Reaction Mechanism



Initially, **3** could be transformed to the saturated 1,4-diketone intermediate **6** via a reduction of the carbon−carbon double bond by $SnCl_2·2H_2O$ in an acid medium.[22] Meanwhile, intermediate **8** could be obtained via hydrolysis of the amide bond of **6**, followed by a decarboxylation.[23] Subsequent intramolecular cyclization/aromatization would then furnish the target molecule **4** via intermediate **9**.[4c,10a]

In summary, we have developed an efficient method for the synthesis of 6-substituted 6*H*-indolo[2,3-*b*]quinolines from mono-*N*-substituted isoindigos in the presence of $SnCl_2·2H_2O$ in acetic acid and a concentrated hydrochloric acid system. This methodology is complementary to previously reported synthetic procedures. It shows wide substrate scope, uses easily available starting materials, and is functional group tolerant. A plausible reduction/hydrolysis/decarboxylation/cyclization/aromatization domino reaction mechanism is proposed. Pyrrole and pyridine rings are synchronously constructed in a one-pot operation in these tetracyclic molecules. It is also found that bis-*N*-substituted isoindigo only gives the corresponding reduction product, 3,3′-bioxindole.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03484.

Synthetic procedure, characterization data, copies of ^{1}H, ^{13}C NMR spectra for compounds **3−5**, **6a** (PDF)

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Crystallographic data for **4d** (CIF)
Crystallographic data for **5** (CIF)

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Notes

The authors declare no competing financial interest.

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