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Iron-Catalyzed Synthesis of Oxindoles: Application to the Preparation of Pyrroloindolines

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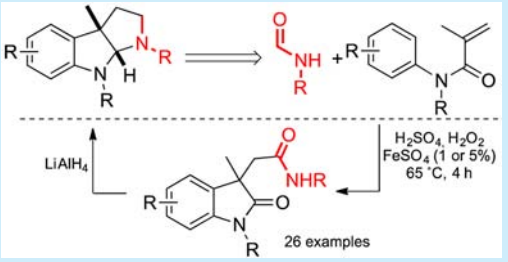
Supporting Information

ABSTRACT: A novel and highly efficient synthetic approach to pyrroloindolines has been developed. The process is based on tandem radical addition/cyclization with inexpensive iron catalyst. This method tolerates a wide range of *N*-methyl-*N*-arylacrylamides as well carbamoyl radicals, providing access to a variety of functionalized 3,3-disubstituted oxindoles, key intermediates for many bioactive pyrroloindolines such as (±)-esermethole, (±)-deoxyeseroline, and (±)-physovenol methyl ether.



The pyrroloindoline skeleton occurs frequently in many alkaloids isolated from various natural sources displaying remarkable biological properties (Figure 1).[1] For instance,

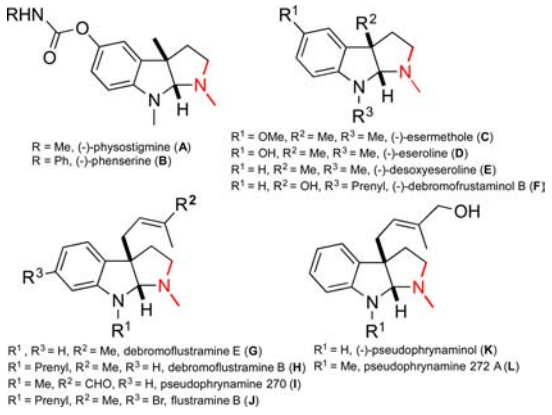


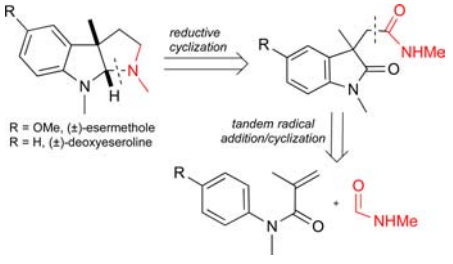
Figure 1. Indole alkaloids named pyrroloindolines.[1,6]

(−)-phenserine (**B**) has been used in the treatment of Alzheimer's disease,[2] and (−)-flustramine B (**J**) exhibits potent anticancer activity.[3] (−)-Physostigmine (**A**) shows physiological effects such as anticholinergic and miotic activities[4] and recently has also shown activity against hepatitis B virus transcription.[5]

The combination of structural features and biological activities presented by natural alkaloids containing the pyrroloindoline ring system makes them attractive targets for development of new methods that allow their construction.[1a,6a,b,d,7] The racemic routes developed so far include Cu(I)-catalyzed vinylation−cyclization,[7i] Wittig olefination−Claisen rearrangement,[8] [3,3]-sigmatropic rearrangement of *N*-aminoskatole derivatives,[9] C-arylation of cyclic amides,[10] palladium-catalyzed intramolecular cyanoamidation, domino Heck−cyanation or cross-coupling reactions,[11] intramolecular aza-Pauson−Khand-type reaction,[12] [4 + 1] cyclization reaction,[13] and oxidative cyclization using hypervalent iodine.[6c,7j] Additionally, asymmetric methods have also been developed to obtain the pyrroloindolines. In general, the asymmetric methods include both transition-metal-catalyzed and organocatalyzed reactions,[3,6a,d,7k−m,14] except for three examples using enzyme-catalyzed reactions.[15] Despite the significant number of approaches for the synthesis of the pyrroloindoline skeleton, they employ several steps and make use of prefunctionalized precursors. Therefore, new synthetic methods able to give access to this ring-system in a short and straightforward fashion using a minimally functionalized precursor would be highly desirable. We envisioned that a method with carbamoyl radical via an Fe-catalyzed radical addition/cyclization would fit such requirements (Scheme 1).

Although acyl radical chemistry has been known for almost a century,[16] the related carbamoyl species were scarcely exploited. Carbamoyl radical generation can be induced by light,[17] a redox system[18] or thermally[19] and has been used for different purposes.[20] Considering that α,β-unsaturated amides

Scheme 1. Retrosynthetic Analysis for Pyrroloindolines



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are reactive toward different radicals, including acyl radical,[21] we proposed the exploitation of such amides with a carbamoyl radical. In our synthetic approach for bioactive pyrroloindolines, the exploitation of such amides with carbamoyl radical would lead to the key intermediates, functionalized 3,3-disubstituted oxindoles.

Initially, we decided to generate the carbamoyl radical using a redox system catalyzed by iron in the presence of sulfuric acid and hydrogen peroxide. Reaction between *N*-methyl-*N*-arylacrylamide **1a** and the carbamoyl radical precursor (formamide or *N*-methylformamide) was chosen as a model to optimize the reaction conditions. The results are summarized in Table 1.

Table 1. Optimization of the Reaction of Carbamoyl Radicals with *N*-Methyl-*N*-arylacrylamide[a]

entry	R	Fe^{2+} (mol %)	yield[b] (%)
1	H	20	70 (**2**)
2	H	10	73 (**2**)
3	H	5	71 (**2**)
4	H	3	55 (**2**)
5	H	1	96 (**2**)
6[c]	H	1	75 (**2**)
7	Me	20	97 (**3**)
8	Me	10	93 (**3**)
9	Me	5	92 (**3**)
10[c]	Me	5	70 (**3**)
11[c]	*n*-Bu	5	<10 (**4**)
12[c,d]	*n*-Bu	5	<10 (**4**)
13[e]	Ph	5	

[a]Reaction conditions: **1a** (1 mmol), H_2SO_4 (1 mmol), H_2O_2 (2 mmol), formamides (5 mL) at 65 °C for 4 h. [b]Conversions were based on GC–MS analysis. [c]2.5 mL of formamides. [d]3 mL of *t*-butyl alcohol. [e]2.5 g of formamide.

The lowest amount of $FeSO_4$ as catalyst (1 mol %) yielded 96% of **2** (Table 1, entry 5). On the other hand, when larger amounts of catalyst were employed, formation of byproducts and decreased formation of desired oxindole **2** were observed (Table 1, entries 1–4). When *N*-methylformamide was used as a carbamoyl radical precursor, higher amounts of catalyst ($FeSO_4$) showed the best yields for **3**, 92–97% (Table 1, entries 7–9). In addition, an attempt to decrease the volume of *N*-methylformamide considerably decreased the conversion to **3** (Table 1, entry 10). Regarding the considerations about catalyst loading versus yield, 5% catalyst (Table 1, entry 9) was selected for further studies. *N*-Butylformamide was also used, and the desired product was observed in low concentration (Table 1, entry 11). We assumed that the heterogeneous system due to the presence of an aqueous solution could be the reason for the low product formation. We then decided to employ *t*-ButOH as cosolvent, a well-known solvent for radical generation. However, once again, the product was observed in very low concentration (Table 1, entry 12), showing that the chemicals solubility is not the main reason for such results. We also applied this system for aromatic formamide, *N*-phenylformamide, which was treated with iron catalyst and H_2O_2 (Table 1, entry 11), but no product was observed, except traces of aniline.

The reaction scope was examined with different *N*-arylacrylamides under the optimized conditions (Figure 2).

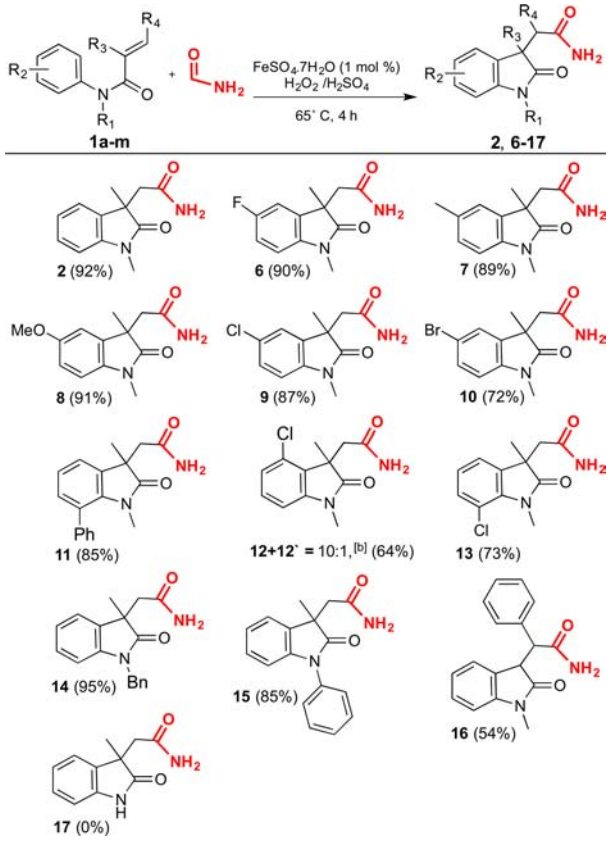

Figure 2. Substrate scope for formamide. (a) Isolated yields. (b) The regioisomeric ratio was determined by ^{1}H NMR.

N-Methyl- and *N*-benzyl-*N*-phenylacrylamides gave the desired oxindoles **2** and **14** in 92 and 95% yields, respectively. Reactions of *N*-methyl-*N*-arylacrylamides containing electron-withdrawing or electron-donating groups at the *para*-position of the aromatic ring afforded oxindoles **6**–**10** in good to excellent yields, 72–91%. *meta*-Substituted *N*-methyl-*N*-arylacrylamide (*m*-chloro) produced a mixture of regioisomers with selectivity of 10:1 (**12**:**12′**) and 64% yield. When *ortho*-substituted *N*-methyl-*N*-arylacrylamides were evaluated, good yields were obtained, even for phenyl or chloro substituents **11** and **13**, respectively (85 and 73% yield). The presence of a free N–H group at the *N*-arylacrylamide resulted in no reaction, and the desired product **17** was not observed.

In sequence, we drove our attention to the reactivity of carbamoyl radical generated from *N*-methylformamide and *N*,*N*-dimethylformamides toward *N*-alkyl-*N*-arylacrylamides (Figure 3).

All *N*-phenylacrylamides containing methyl, benzyl, or phenyl groups at the nitrogen were able to be transformed into the corresponding oxindoles with excellent results (i.e., **3**, **26**, and **27**). *N*-Methyl-*N*-arylacrylamides containing electron-withdrawing and electron-donating groups at the *para*-position of the aromatic ring also gave oxindoles **18**–**22** in excellent yields, 88–95%. When *ortho*-substituted *N*-methyl-*N*-arylacrylamides were evaluated, good yields were obtained (**23** = 81% and **25** = 65% yield). The use of chlorine *meta*-substituted *N*-

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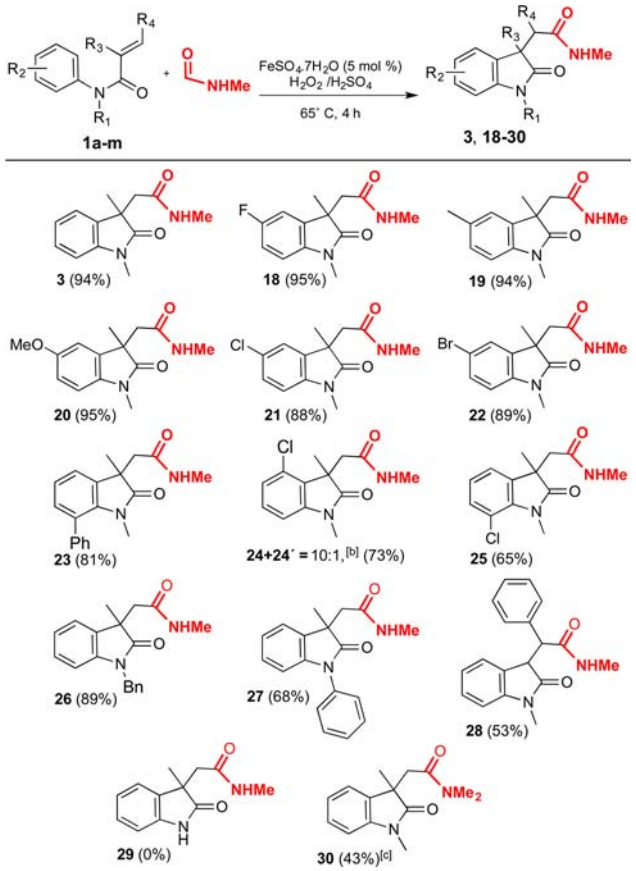


Figure 3. Substrate scope for *N*-methylformamide. (a) Isolated yields. (b) The regioisomeric ratio was determined by ^{1}H NMR. (c) Dimethylformamide was used as starting material.

methyl-*N*-arylacrylamide as a substrate gave a mixture of regioisomers with selectivity **24**:**24′** = 10:1 and 73% yield. Once again, the *N*-arylacrylamide with a free NH group did not provide the desired product, **29**. Dimethylformamide (DMF) was also used, and the carbamoyl radical was able to produce the oxindole **30** in 43% yield.

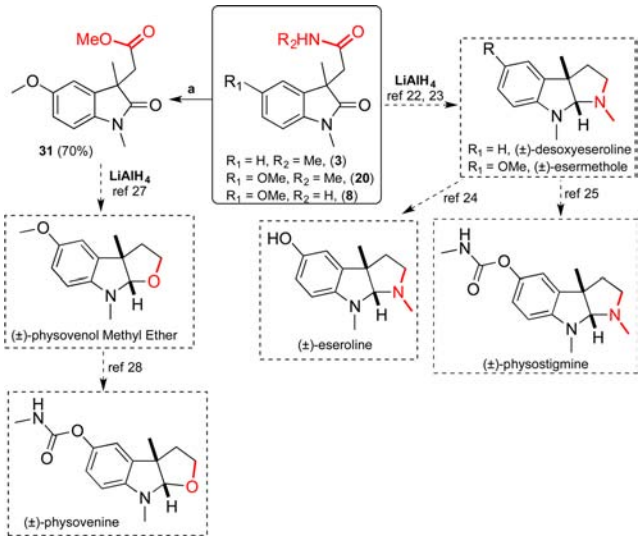
To demonstrate the strength of our method and how this approach can be very useful as a general method for preparing pyrroloindoles, we selected some natural products to show their formal synthesis (Scheme 2).

The oxindoles **3** and **20**, which were obtained from reactions between *N*-methyl-*N*-arylacrylamides and the appropriate carbamoyl radical precursors (Figure 3), could be a synthetic intermediate to (±)-esermethole,[22] (±)-deoxyeseroline,[23] (±)-eseroline,[24] and (±)-physostigmine.[25] Another application of our strategy involved the esterification of oxindole **8** with thionyl chloride and methanol to afford the methyl ester **31** (70% yield).[26] This compound could be transformed in a few steps, into indole alkaloid (±)-physovenol methyl ether.[27] In this case, a system called furoindoline would be prepared using our approach.[6b] Physovenol methyl ether could also be an intermediate to the natural product (±)-physovenine.[28]

A plausible mechanism for the tandem radical addition/cyclization reaction between carbamoyl radical and *N*-alkyl-*N*-arylacrylamide is depicted (Scheme 3).[18]

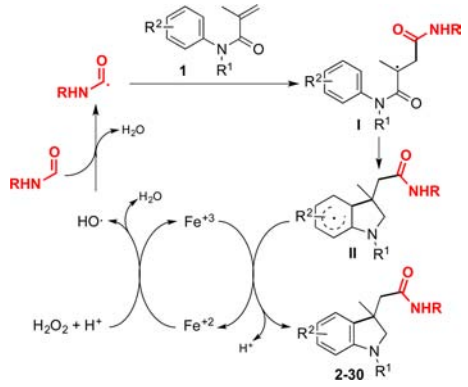
In a Fenton-type reaction, hydrogen peroxide reacts with iron(II), under heating in acidic medium, to produce iron(III), hydroxyl radical, and water. The hydroxyl radical formed, which has a high oxidation potential, abstracts a hydrogen from the

Scheme 2. Formal Synthesis of Some Natural Products[a]



[a]Reaction conditions: (a) $SOCl_2$, MeOH (70% yield).

Scheme 3. Proposed Reaction Mechanism



formamide, generating the carbamoyl radical. Then, the carbamoyl radical adds to the double bond of the α,β-unsaturated system **1**, yielding a tertiary carbon-centered radical species **I**, which undergoes an intramolecular cyclization with the aromatic ring, generating the cyclic radical **II**. The rearomatization of the cyclic radical **II** involves the reduction of iron(III) to iron(II) and concomitant loss of a proton, regenerating the aromaticity of the benzene ring to produce the corresponding oxindoles.[21]

In conclusion, we have developed a tandem radical addition/cyclization method with inexpensive iron catalysts, which provides an easy access to a variety of functionalized 3,3-disubstituted oxindoles. This method tolerates a wide range of *N*-alkyl-*N*-arylacrylamides as well carbamoyl radicals generated from formamide and *N*-methylformamide. The functionalized 3,3-disubstituted oxindoles are key intermediates for the direct synthesis of bioactive pyrroloindolines using only a reductive cyclization protocol. In fact, our synthetic approach is the shortest route described so far for the preparation of pyrroloindolines, from the easily accessible *N*-aryl-*N*-acrylamides, obtained from the commercial available anilines.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedure, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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