

### Fe(OTf)<sub>3</sub>-Catalyzed Aromatization of Substituted 3-Methyleneindoline and Benzofuran Derivatives: A Selective Route to C-3-Alkylated Indoles and Benzofurans

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A simple and convenient approach was developed to the selective synthesis of 3-substituted indoles and benzofurans by the isomerization of 3-methyleneindoline and benzofuran derivatives catalyzed by  $Fe(OTf)_3$ . The salient features of this method are the easy availability of substrates, high yield,

Introduction

Indoles and benzofurans are common structural motifs found in numerous natural products, pharmaceutical agents, functional materials, and agrochemicals.<sup>[1,2]</sup> Therefore, the synthesis of substituted indoles and benzofurans has attracted great interest.<sup>[3,4]</sup> Among the family of substituted indoles, C-3-substituted indoles are the key structural units of many promising therapeutic agents<sup>[5]</sup> such as anticancer, antimigraine, antidepressant, anti-inflammatory, antiestrogen, and antagonist drugs. Moreover, C-3-substituted indoles are also very useful for the construction of many biologically active compounds.<sup>[6]</sup>

Consequently, numerous synthetic methods have been developed for the preparation of C-3-alkylindoles,<sup>[7]</sup> such as substitution of indole with alkyl halides in the presence of acids or bases, conjugate addition of indoles to  $\alpha$ ,  $\beta$ -unsaturated compounds, direct substitution of  $\pi$ -activated alcohols with indoles or epoxides and aziridine ring opening by indoles in the presence of various metal catalysts and Brønsted acids. Besides these, procedures involving the generation of reactive alkylideneindolenine intermediates followed by selective nucleophilic addition have also been developed to produce a large array of 3-substituted indoles.<sup>[8]</sup> Very recently, Beller et al. reported ruthenium-catalyzed carbon-carbon bond formation between indole and benzylic and aliphatic amines.<sup>[9]</sup> Yus and co-workers developed a noncatalytic C-3 alkylation using activated benzyl alcohol through a hydrogen-transfer strategy with an excess amount of KOH.<sup>[10]</sup> Armstrong et al. described a Sc(OTf)<sub>3</sub>- mild reaction conditions, tolerance of a variety of functional groups, and use of an environmentally friendly catalyst. A possible mechanism has also been proposed for the isomerization process.

catalyzed nucleophilic substitution of indolylmethyl Meldrum's acids.<sup>[11]</sup> Intermolecular hydroarylation of indoles with alkenes in the presence of [(PPh<sub>3</sub>)AuCl]/AgOTf<sup>[12a]</sup> and with alkynes in the presence of ruthenium complexes/ TFA<sup>[12b]</sup> have also been demonstrated.

However, many of these methods involve strongly acidic conditions, expensive and toxic reagents, complex handling, and result in low yields of products. Moreover, in all these methods indoles have been used as starting material, so the methods suffer from unavailability of suitably substituted indole derivatives. Thus, it is highly desirable to develop a catalytic method to furnish functionalized 3-alkyl-substituted indoles from easily available starting materials.

In continuation of our ongoing program in developing environmentally friendly and inexpensive iron-catalyzed syntheses of heterocyclic molecules,<sup>[13]</sup> we thought that the simple aromatization of 3-methyleneindoline derivatives would be a very selective and practical method for the synthesis of C-3-substituted indole derivatives (Scheme 1). However, literature search reveals that, although plenty of methods are available for the synthesis of various indole derivatives by means of palladium-catalyzed reactions from aniline derivatives,<sup>[3d,14]</sup> no selective method has been developed for the synthesis of C-3-substituted indole derivatives. During our recent study on the synthesis of benzo[*b*]carbazole derivatives,<sup>[131]</sup> we observed that these reaction conditions did not work for substituted 3-methyleneindoline de-



Scheme 1. Synthetic strategies for 3-substituted indoles.

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### **Results and Discussion**

The required starting material, 3-methyleneindoline derivative **2**, was prepared in high yield by using our previous method involving a domino Heck–Suzuki coupling of 2bromo-*N*-propargylanilide **1** with arylboronic acid derivatives, as outlined in Scheme 2.<sup>[13f]</sup> After having a series of 3-methyleneindoline derivatives **2**, we next tried to optimize the reaction conditions for the isomerization of 3-methyleneindoline derivatives.



Scheme 2. Preparation of substituted 3-methyleneindolines. Reaction conditions:  $Pd(OAc)_2$  (5 mol-%),  $PCy_3$  (10 mol-%),  $K_2CO_3$  (2.5 M), EtOH, toluene, reflux.

At first, a large number of Lewis and Brønsted acids were screened by using 2a as the model substrate (Table 1). We first examined the isomerization of 2a to 3a in the presence of FeCl<sub>3</sub> (10 mol-%) at 80 °C in 1,2-dichloroethane; however, no reaction took place even after prolonged heating (Table 1, entry 1). Interestingly, we noticed that when the reaction mixture was heated to 135 °C in chlorobenzene a trace amount of isomerized product 3a was formed after heating for 12 h (Table 1, entry 2).

Encouraged by these results, we then screened other commonly used iron salts such as FeBr<sub>3</sub> and Fe(OTf)<sub>3</sub> for this transformation. We found that FeBr<sub>3</sub> did not initiate the reaction, whereas Fe(OTf)<sub>3</sub> (10 mol-%) gave 90% yield at 60 °C within 3 h. Moreover, we also observed that the reaction was sluggish when we reduced the amount of Fe(OTf)<sub>3</sub>, and further increasing the amount of catalyst did not improve the yield. Next, we also screened other metal salts such as In(OTf)<sub>3</sub>, AgOTf, and AgSbF<sub>6</sub>; we found that  $In(OTf)_3$  did not work under similar conditions, but the isomerization took place with AgOTf (10 mol-%) and AgSbF<sub>6</sub> (10 mol-%) at 60 °C and gave product 3a in 73% and 76% yields, respectively (Table 1, entries 6 and 7). Brønsted acids such as *p*-toluenesulfonic acid monohydrate (PTSA·H<sub>2</sub>O) and triflic acid (TfOH) also afforded the desired products, but not in higher yields (74% and 82%) (Table 1, entries 8 and 9). Finally, we also tested this isomerization with stoichiometric amounts of bases such as K<sub>3</sub>PO<sub>4</sub> in DMF at 100 °C (Table 1, entry 10). Although, this strategy has been reported for the synthesis of 3-substituted benzofuran derivatives,<sup>[15]</sup> it did not work for the synthesis of indole derivative 3a. These results demonstrated that Fe(OTf)<sub>3</sub> has higher catalytic activity for this transforTable 1. Optimization of reaction conditions for the isomerization of 2a to indole derivative 3a.<sup>[a]</sup>



Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield (%) <sup>[b]</sup>
1	FeCl <sub>3</sub>	1,2-dichloroethane	80	10	n.r.
2	FeCl <sub>3</sub>	chlorobenzene	135	10	15
3	FeBr <sub>3</sub>	1,2-dichloroethane	80	6	n.r.
4	Fe(OTf) <sub>3</sub>	1,2-dichloroethane	60	3	90
5	In(OTf) <sub>3</sub>	1,2-dichloroethane	60	6	n.r.
6	AgOTf	1,2-dichloroethane	60	6	73
7	AgSbF <sub>6</sub>	1,2-dichloroethane	60	4	76
8	PTSA∙H <sub>2</sub> O	1,2-dichloroethane	60	5	74
9	TfOH	1,2-dichloroethane	60	3	82
10	K <sub>3</sub> PO <sub>4</sub>	dimethylformamide	100	7	n.r.

[a] Reaction conditions: Substrate **2a** (0.23 mmol), 1,2-dichloroethane (2 mL), catalyst (0.023 mmol). [b] Isolated yield of pure product.

mation. A moderately strong Lewis acid is probably more efficient for this transformation. Thus,  $Fe(OTf)_3$  (10 mol-%) in 1,2-dichloroethane at 60 °C was defined as the optimal reaction conditions for further study.

Next, the isomerization of a large array of 3-methyleneindoline derivatives 2a-2i was investigated under these reaction conditions; the results are presented in Table 2. We were pleased to observe that this isomerization process was quite general and smoothly afforded a variety of disubstituted and monosubstituted alkylideneindole derivatives in very good to excellent yields. The reaction was not markedly affected by the substituents on any of the aryl rings. For example, aryl rings (R<sup>4</sup>) including those bearing an electron-donating group such as p-OMe (Table 2, entries 3 and 4) and electron-withdrawing groups such as p-Cl and p-COMe (Table 2, entries 5, 6 and 7) were compatible, and all gave the corresponding C-3-substituted indoles in good to excellent yields. Functional groups such as -CHO, -COMe, and -Cl are very useful for further synthetic transformations to construct a library of C-3-substituted indole derivatives for biological studies. Similarly, both substituted and unsubstituted aryl rings  $(R^3)$  were also tolerated and gave high yields of the desired products.

Moreover, aryl- and alkyl-substituted alkylideneindole derivative **2h** (Table 2, entry 8) was also smoothly converted into the desired C-3-substituted indole derivative **3h** in good yield. In addition, monosubstituted alkylideneindole derivative **2i** (Table 2, entry 9) could also be aromatized to 3-



Table 2. Fe(OTf)\_3-catalyzed isomerization of  $2a{-}2j$  to C-3-substituted indoles  $3a{-}3j.^{\rm [a]}$ 

			R <sup>4</sup> _R <sup>3</sup>			$R^4$	
	F	र <sup>1</sup>		Fe(OTf) <sub>3</sub> ,	60 °C		
			$\sim N$ $R^2$	1,2-010110106	enane	$\sim$ N $R^2$	
Entry	/ R <sup>1</sup>	R2	a– <b>2</b> j	P <sup>4</sup>	Timo	3a–3j Product Yi	eld (%) <sup>[b]</sup>
			IX	N	TITLE	Ph	
1	н	Ts	Ph	Ph	3		90
2	5-Me	Ts	Ph	Ph	3		89
3	5-F	Ts	Ph	<i>p</i> -OMeC <sub>6</sub> H₄	3	F 3 <sup>o</sup> Ph <sup>1S</sup> C <sub>6</sub> H <sub>4</sub> -p-OMe N 3 <sup>c</sup> <sub>Db</sub> Ts	96
4	н	Ts	Ph	<i>p</i> -OMeC <sub>6</sub> H₄	2.5	<sup>r</sup> <sup>II</sup> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OMe <sup>3d</sup> PhTs PhTs	97
5	н	Ts	p-CIC <sub>6</sub> H <sub>4</sub>	Ph	5	3 <sup>e</sup> Ph <sup>Ts</sup> and a set	82
6	н	Ts	<i>p</i> -COMeC <sub>6</sub> ⊦	l <sub>4</sub> Ph	4		83
7	н	Ts	Ph	p-CHOC <sub>6</sub> H₄	4	<sup>r</sup> <sup>II</sup> , C <sub>6</sub> H <sub>4</sub> -p-CHO <sup>3g</sup> <sub>Ph</sub> Ts	81
8	н	Ts	<i>n</i> -Pr	Ph	7	3h Ts <sub>Db</sub>	72
9	5-F	Ts	Н	Ph	3.5	F N 3i Ph Ts C-H - PcCl	75
10	н	Ms	p-CI-C <sub>6</sub> H <sub>4</sub>	Ph	2.5		99

[a] Reaction conditions: Substrate (0.23 mmol) and 1,2-dichloroethane (2 mL). [b] Isolated yield of pure product.

benzyl indole derivative **3i** in 75% yield in the presence 10 mol-%  $Fe(OTf)_3$ . Further study shows that, instead of *N*-Ts derivative **2j** (Table 2, entry 10), the substrate containing *N*-Ms also worked smoothly and gave the desired 3-alkylindole derivative **3j** in quantitative yield.

Furthermore, we also applied this methodology to the synthesis of 3-alkylbenzofurans. To our delight, the reactions proceeded smoothly in the presence of 10 mol-% Fe(OTf)<sub>3</sub>, affording the corresponding 3-alkylbenzofurans **5a–5d** (Table 3) in good to excellent yields. This aromatization was not affected by the presence of a variety of functional groups such as *p*-OMe, *m*-CF<sub>3</sub>, and *m*-NO<sub>2</sub> on aryl ring R<sup>1</sup>. This method was also very efficient for the synthesis of naphthyl-substituted benzofuran derivative **4e** in 92% yield (Table 3, entry 5). Compared to a recently developed method for the aromatization of 2,3-dihydro-methyl-enebenzofuran derivatives in basic medium that required

stoichiometric amounts of bases such as  $K_3PO_4$  in DMF solvent at 100 °C, the present method is superior as only catalytic amounts (10 mol-%) of an environmentally friendly iron salt is required and it works at lower temperature (60 °C).

Table 3. Fe(OTf)\_3-catalyzed isomerization of 4a-4d to C-3-substituted benzofurans  $5a-5d.^{\rm [a]}$ 



[a] Reaction conditions: Substrate (0.23 mmol), catalyst (0.023 mmol), and 1,2-dichloroethane (2 mL). [b] Isolated yield of pure product.

Therefore, an Fe(OTf)<sub>3</sub>-catalyzed isomerization of 3methyleneindoline and benzofuran derivatives to corresponding 3-substituted indoles and benzofuran derivatives is very straightforward. Fe(OTf)<sub>3</sub> was found to be the best among the catalysts studied. Fe(OTf)<sub>3</sub> was prepared from FeCl<sub>3</sub> (99.5%) and TfOH according to a literature procedure.<sup>[16]</sup> Moreover, we noticed that TfOH was also effective for this transformation and gave 82% yield (Table 1, entry 9); hence, there was a chance that this reaction may also be catalyzed by in situ generated TfOH. To check this, we carried out this reaction in the presence of a sterically hindered non-nucleophilic base such as 2,6-di-*tert*-butyl-4methylpyridine (Scheme 3). We observed that no significant



b) Reaction was performed in the absence of Fe(OTf)<sub>3</sub>.

Scheme 3. Study of the reaction in the presence of a combination of  $Fe(OTf)_3$  and base.

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changes occur when we added pyridine as base in combination with  $Fe(OTf)_3$ . The combination of catalysts also gave a high yield of the desired product, but no such isomerization took place in the presence of pyridine base. So, we concluded that possibly TfOH was not generated during the course of the reaction and  $Fe(OTf)_3$  was the real catalyst for this transformation.

A plausible mechanism for the isomerization, based on the above experimental observations, is shown in Scheme 4. We believe that iron(III) triflate coordinates to the double bond of **2a** and thus polarizes the alkene double bond. This activation triggers the deprotonation of the  $-CH_2$ - group, leads to the isomerization of the double bond, and affords iron-bound product **2a**'. Then, demetalation of **2a**' by rapid protonolysis releases indole derivative **3a** and regenerates Fe(OTf)<sub>3</sub> for the next catalytic cycle.



Scheme 4. Plausible mechanism for the isomerization of 2a.

### Conclusions

We have developed an Fe(OTf)<sub>3</sub>-catalyzed synthesis of 3alkylindole and 3-alkylbenzofuran derivatives in good to high yields under mild conditions from 3-methyleneindoline and benzofuran derivatives. A variety of functionalized 3alkylidene indole and benzofuran derivatives could easily be prepared by a palladium-catalyzed domino Heck–Suzuki coupling reaction. The advantages of this methodology are easily available starting materials, toleration of various functional groups, excellent regioselectivity, and the use of an environmentally friendly and inexpensive iron catalyst. In view of the mild reaction conditions and broad functional group tolerance, we expect that this reaction will be useful for the synthesis of biologically significant 3-substituted indoles and benzofurans.

### **Experimental Section**

**General Procedure:** To a solution of **2a** (or **4a**) in dry 1,2-dichloroethane was added anhydrous  $Fe(OTf)_3$ . The mixture was stirred at 60 °C under an argon atmosphere for 3 h. After completion of the reaction (monitored by TLC), the solvent was evaporated, and the product was purified by column chromatography (silica gel 60–120 mesh) and eluted with pet ether (60–80 °C)/EtOAc (97:3, v/v) to afford compound **3a** (or **5a**). The product was characterized by <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy as well as HRMS.

**Supporting Information** (see footnote on the first page of this article): Full experimental details and <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds are provided.

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