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PAPER

$FeCl_3$-promoted alkylation of indoles by enamides†

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An efficient iron-promoted alkylation of indoles with enamides has been accomplished under mild reaction conditions. The reaction proceeded with remarkable regioselectivity leading exclusively to substitution by indoles at α-position of enamides.

Introduction

The hydroarylation of alkenes is one of the most important reactions for the functionalization of arenes and heteroarenes.[1] One important application of this transformation is the alkylation of indoles, which are key structural motifs of numerous natural products and biologically active compounds.[2] Although Friedel–Crafts reactions are well-known transformations for alkylation, the methods often suffer from drastic reaction conditions (high reaction temperature, strong acidic/base conditions) and regioselectivity problems.[3] In recent years, the transition-metal catalyzed process has emerged as an attractive alternative to the conventional Friedel–Crafts reaction, and $Cu(OTf)_2$,[4] $CeCl_3$,[5] $Zn(OTf)_2$,[6] $InBr_3$,[7] SmI_3,[8] $Sc(OTf)_3$,[9] $PtCl_2$,[10] or $AuCl_3$[11] catalytic systems have been developed. These processes have been proved remarkably effective under mild reaction conditions and enjoy a broad application in the synthesis of alkylated indoles. However, most of these investigations focus on the addition of indoles to electron-neutral alkenes or electron-deficient alkenes, which are activated by a conjugated electron-withdrawing group. There has been only scant attention in developing a general methodology for the addition of indoles to electron-rich alkenes such as enamides.[12] To the best of our knowledge, the metal-catalyzed addition of indoles to enamides has not been explored. The development of an efficient procedure for the alkylation of indoles with electron-rich olefins such as enamides under mild conditions is highly desired.

Recently, iron has been increasingly explored in organic transformations as an inexpensive and environmentally benign catalyst.[13] There have been a series of reports concerning novel iron-catalyzed reactions, which lead to efficient $C(sp^2)$–$C(sp^3)$,[14] $C(sp^2)$–$C(sp^2)$,[15] $C(sp^2)$–$C(sp)$,[16] and C–N[17] bond formations. Herein, we report a highly efficient method for the addition of indoles to enamides in the presence of an iron catalyst under mild reaction conditions (Scheme 1). This facile catalytic system was also applicable to indolizines.

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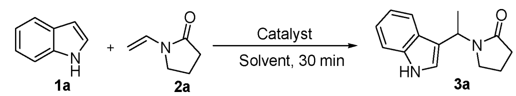
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds along with copies of ^1H and ^{13}C NMR spectral data. See DOI: 10.1039/c0ob00709a

Table 1 Optimization of reaction conditions[a]

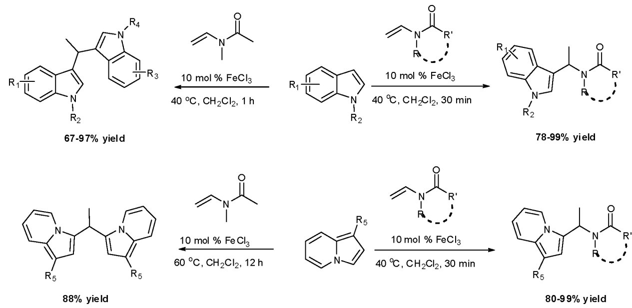


Entry	Catalyst	Solvent	$T/°C$	Yield (%)[b]
1	none	CH_2Cl_2	40	n.r
2	$ZnCl_2$	CH_2Cl_2	40	n.r
3	$RuCl_3$	CH_2Cl_2	40	trace
4	$InBr_3$	CH_2Cl_2	40	n.r
5	$NiCl_2·6H_2O$	CH_2Cl_2	40	42
6	$SnCl_4$	CH_2Cl_2	40	41
7	$CuCl_2$	CH_2Cl_2	40	90
8	$BF_3·Et_2O$	CH_2Cl_2	40	89
9	$FeCl_3$	CH_2Cl_2	40	99 (98)[c]
10	$FeCl_3·6H_2O$	CH_2Cl_2	40	97
11	Fe_2O_3	CH_2Cl_2	40	32
12	$FeCl_2$	CH_2Cl_2	40	trace
13	$Fe(acac)_3$	CH_2Cl_2	40	n.r
14[d]	HCl	CH_2Cl_2	40	77
15	TMSCl	CH_2Cl_2	40	74
16	HOAc	CH_2Cl_2	40	n.r
17	$FeCl_3$	CH_2Cl_2	r.t.	53
18	$FeCl_3$	DMF	40	n.r
19	$FeCl_3$	CH_3CN	40	86
20	$FeCl_3$	THF	40	78
21	$FeCl_3$	toluene	40	70
22	$FeCl_3$	acetone	40	80
23	$FeCl_3$	H_2O	40	78

[a] Reaction conditions: indole (0.5 mmol), 1-vinyl-2-pyrrolidinone (0.6 mmol), catalyst (0.05 mmol), solvent (5 ml), 40 °C, 30 min. [b] Isolated yields based on indole. [c] The isolated yield in anhydrous CH_2Cl_2 under nitrogen atmosphere is given in parentheses. [d] Concentrated hydrochloric acid (wt%: 36.5%) was used.

Results and discussion

In our initial studies, we tested the effect of various metals on the addition of indole (**1a**) toward enamide (**2a**) in CH_2Cl_2. As shown in Table 1, no reaction was observed in the absence of metal catalyst (Table 1, entry 1). Treatment of **1a** and **2a** with $ZnCl_2$, $RuCl_3$ or $InBr_3$ failed to give any product at 40 °C for 30 min (Table 1, entries 2–4). The desired addition product 1-(1-(1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (**3a**) was isolated when $NiCl_2·6H_2O$ or $SnCl_4$ were applied as catalysts, but with very



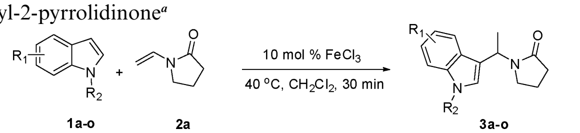
Scheme 1 Iron-catalyzed alkylation of indoles and indolizines with enamides.

low yields (Table 1, entries 5–6). A more promising result was obtained by the use of 10 mol% $CuCl_2$ (Table 1, entry 7). When $BF_3{\cdot}Et_2O$ was applied, 89% yield was isolated (Table 1, entry 8). Further exploration led to a discovery that a 99% isolated yield was obtained by employing $FeCl_3$ as catalyst (Table 1, entry 9). Importantly, the reaction was carried out in open air without exclusion of oxygen from the reaction flask, and $FeCl_3{\cdot}6H_2O$ showed almost the same reactivity with $FeCl_3$ (Table 1, entry 10). In contrast, iron reagents such as Fe_2O_3, $FeCl_2$ and $Fe(acac)_3$ were inactive (Table 1, entries 11–13), showing that the source of iron species influenced the reaction significantly. Catalytic amounts (10 mol%) of Brønsted acids delivered no or relatively lower product yields (Table 1, entries 14–16). The reaction could be performed at room temperature in lower yield (Table 1, entry 17). The solvents are crucial to the reaction. No reaction was observed in DMF (Table 1, entry 18). The comparable results were obtained by the use of CH_3CN, toluene, acetone, and THF as solvent (Table 1, entries 19–22). It should be noted that the reaction could carried out in water to give a 78% yield in 40 °C for 30 min (Table 1, entry 23).

Under the optimized reaction conditions, we examined the reactivity of various indoles as summarized in Table 2. In general, indoles with both electron-rich and electron-deficient substituents are active to give the adducts in high yields. Indoles with an electron-donating group were highly active to afford the alkylated indoles in excellent yields at 40 °C within 30 min (Table 2, entries 1–6). The indoles with *C2* substituents delivered the corresponding alkylated indoles in high yields (Table 2, entries 7–8), illustrating that steric hindrance played a poor role to the reaction. Indole with moderate electron-withdrawing bromide group was active also to afford the corresponding alkylated indole in 98% yield (Table 2, entry 9). However, the strong electron-withdrawing substituents in indoles led to the decrease of the reaction rate, and the prolongation of the reaction time was needed to access the high yields (Table 2, entries 10–12). *N*-Substituted indoles presented equally high efficiency in respect to that of free indoles to give the adducts in high yields (Table 2, entries 13–15). Furthermore, this facile catalytic system was also applicable to various indolizines (Table 2, entries 16–18).

The reactivity of various enamindes was examined and the results are summarized in Table 3. Satisfying results were obtained when 1-vinylpyrrolidin-2-one **2a** was replaced with 1-vinylazepan-2-one **2b** (Table 3, entries 1–3). However, *N*-vinylformamide **2c** gave the corresponding products in low yields under the reaction conditions. To our delight, when the ratio of the substrates was

Table 2 Iron-catalyzed direct alkylation of indoles and indolizidines with 1-vinyl-2-pyrrolidinone[a]



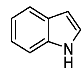
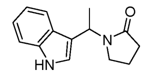
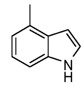
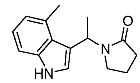
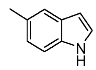
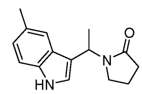
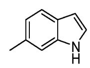
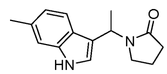
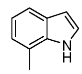
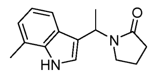
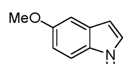
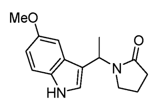
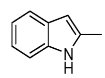
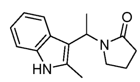
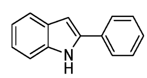
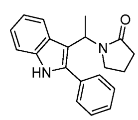
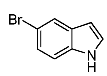
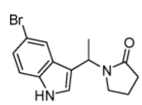
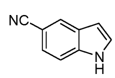
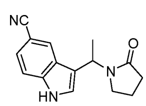
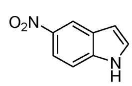
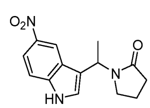
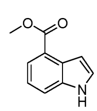
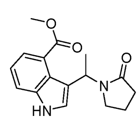
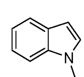
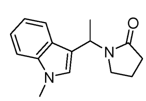
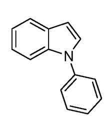
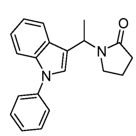
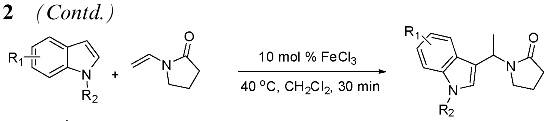
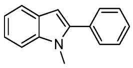
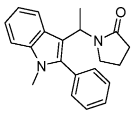
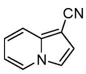
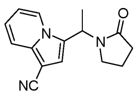
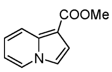
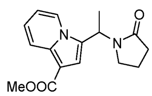
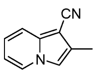
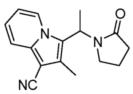
Entry	Indole/indolizine	Product	Yield (%)[b]
1	 **1a**	 **3a**	99
2	 **1b**	 **3b**	82
3	 **1c**	 **3c**	78
4	 **1d**	 **3d**	96[c]
5	 **1e**	 **3e**	95
6	 **1f**	 **3f**	88
7	 **1g**	 **3g**	96
8	 **1h**	 **3h**	90
9	 **1i**	 **3i**	98
10	 **1j**	 **3j**	99[d]
11	 **1k**	 **3k**	83[d]
12	 **1l**	 **3l**	86
13	 **1m**	 **3m**	98
14	 **1n**	 **3n**	97

Table 2 *(Contd.)*

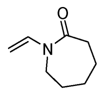
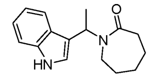
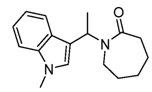
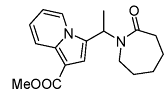
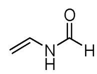
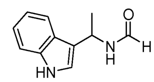
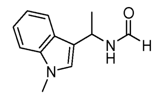
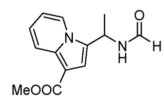
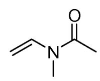
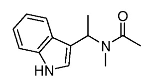
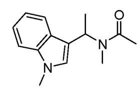
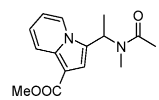


1a-o 2a 3a-o

Entry	Indole/indolizine	Product	Yield (%)[b]
15	 **1o**	 **3o**	88
16	 **1p**	 **3p**	95
17	 **1q**	 **3q**	99
18	 **1r**	 **3r**	92

[a] Reaction conditions: indoles (0.5 mmol), 1-vinyl-2-pyrrolidinone (0.6 mmol), $FeCl_3$ (8 mg, 0.05 mmol), in CH_2Cl_2 (5 ml), 40 °C, 30 min. [b] Isolated yields based on indole. [c] 6-Methyl-1*H*-indole (0.75 mmol), 1-vinyl-2-pyrrolidinone (0.5 mmol), isolated yields based on *N*-vinylformamide, 3 h was used. [d] The reaction time was 6 h.

Table 3 Iron-catalyzed direct alkylation of indoles and indolizines with various enamides[a]

Entry	Enamide	Indole/indolizine	Product	Yield (%)[b]
1	 **2b**	**1a**	 **4a**	90
2	**2b**	**1m**	 **4b**	91
3	**2b**	**1q**	 **4c**	99[c]
4[d]	 **2c**	**1a**	 **5a**	97 67[e] 81[f]
5[d]	**2c**	**1m**	 **5b**	99
6[d]	**2c**	**1q**	 **5c**	99
7	 **2d**	**1a**	 **6a**	79[g]
8	**2d**	**1m**	 **6b**	81
9	**2d**	**1q**	 **6c**	80[c]

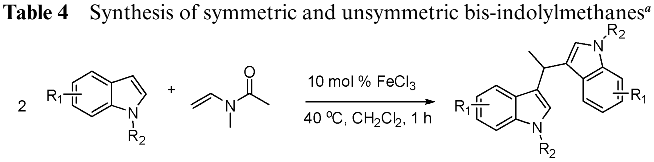
[a] Reaction conditions: indoles (0.5 mmol), enamides (0.6 mmol), $FeCl_3$ (8 mg, 0.05 mmol), in CH_2Cl_2 (5 ml), 40 °C, 30 min. [b] Isolated yields based on indole. [c] 3 h, 60 °C, were used. [d] Indole (0.75 mmol), *N*-vinylformamide enamide (0.5 mmol), isolated yields based on *N*-vinylformamide. [e] Isolated yield when concentrated HCl (10 mol %) was used as catalyst. [f] Isolated yield when TMSCl (10 mol%) used as catalyst. [g] The reaction was at room temperature.

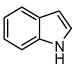
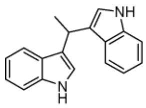
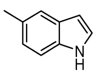
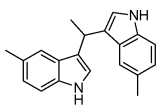
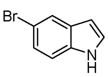
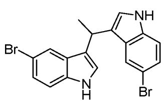
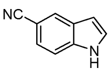
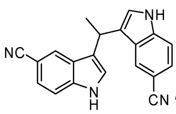
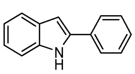
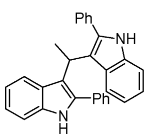
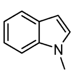
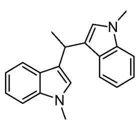
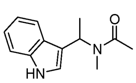
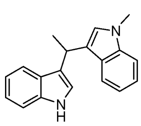
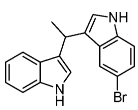
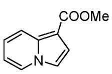
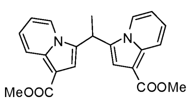
modified from indole : enamide = 1 : 1.2 to enamide : indole = 1 : 1.5, the reaction was dramatically improved to afford the products in excellent yields (Table 3, entries 4–6). *N*-Methyl-*N*-vinylacetamide **2d** afforded low yield in the reaction with *N*-free indole **1a** possibly due to the decomposition of the product, and a 79% yield was obtained when the reaction was performed at room temperature (Table 3, entry 7). On the contrary, *N*-methyl indole **1m** participated in the reaction smoothly to afford **6b** in 81% yield at 40 °C within 30 min (Table 3, entry 8). In the case of indolizine **1q**, longer reaction time and higher temperature were required (Table 3, entries 3 and 9).

During the study of the reaction of indoles with *N*-methyl-*N*-vinylformamide **2d**, we found that the ratio of indoles to enamides influenced the final products. An excess of indole led to the substitution of indoles to **2d** to give a mixture of alkylated indole **6a** and a second alkylation product of bis-indolylmethane **7a**. Since bis-indolylmethane and its derivatives are key structural units in many natural drugs used as cancer growth inhibitors,[18] we investigated the reaction conditions for selective formation of bis-indolylmethane products as shown in Table 4. It was found that the amount of indole played a key role for the second alkylation. When 3 equivalents of indole were used, only bis-indolylmethane **7a** was obtained in 91% yield (Table 4, entry 1). This transformation was compatible with a broad of functional groups, including –CH_3, –Br, –CN, and *N*–CH_3 (Table 4, entries 2–6). Importantly, asymmetric bis-indolylmethanes could be prepared by the use of **6a** as initial substrate (Table 4, entry 7–8). The reaction was also applicable to indolizine (Table 4, entry 9). The enamides **2a**, **2b**, and **2c** failed to furnish the bis-indolylmethane under the reaction conditions.

There are two possible pathways for the intermolecular C-3 indole alkylation as shown in Scheme 2. (1) With the aid of Lewis acid $FeCl_3$, enamide **2a** transforms to the iminium species **I**, which reacts with indole **1a** *via* a Friedel–Crafts-type process to afford the alkylation product **3a** (Scheme 1, path **A**).[19] (2) The protonation of enamide **2a** by the Brønsted acid hydrolyzed from $FeCl_3$ generates the iminium **II**, which undergoes nucleophilic addition with indoles to give the final product (Scheme 1, path **B**).[12,20] We performed the reaction in anhydrous CH_2Cl_2 under nitrogen atmosphere, and it was found that a high yield of desired product 1-(1-(1*H*-indol-3-yl)ethyl)pyrrolidin-2-one **3a** was obtained (Table 1, entry 9). Furthermore, typical Lewis acid $BF_3{\cdot}Et_2O$ also worked well in this transformation (Table 1, entry 8). On the other hand,

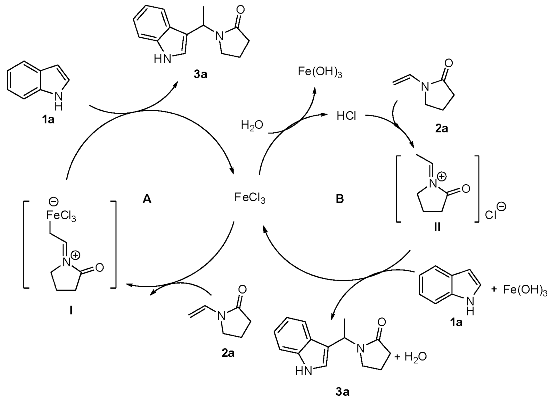
Table 4 Synthesis of symmetric and unsymmetric bis-indolylmethanes[a]



Entry	Indole/indolizine	Product	Yield (%)[b]
1	 **1a**	 **7a**	91
2	 **1c**	 **7b**	89
3	 **1i**	 **7c**	88[c]
4	 **1j**	 **7d**	67[d]
5	 **1h**	 **7e**	75
6	 **1m**	 **7f**	90
7	 **6a**	 **7g**	97
8	**6a**	 **7h**	96
9	 **1q**	 **7i**	88[e]

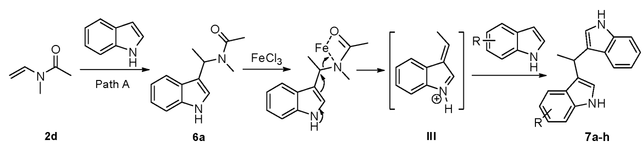
[a] Reaction conditions: indoles (1.5 mmol), *N*-methyl-*N*-vinylacetamide (0.5 mmol), $FeCl_3$ (8 mg, 0.05 mmol), in CH_2Cl_2 (5 ml), 40 °C, 1 h. [b] Isolated yields based on *N*-methyl-*N*-vinylacetamide. [c] The reaction time prolongs to 5 h. [d] 12 h was used. [e] The reaction was in 60 °C for 12 h.

the employment of hydrochloric acid (10 mol%) and trimethyl chlorosilane (TMSCl) (10 mol%) as catalysts resulted in the desired products with enamide **2a** and **2c** in moderate yields (Table 1, entries 14 and 15; Table 4, entry 4), and the reaction with enamides **2b** and **2d** failed. Thus, we postulate the reaction takes place mainly through path **A**.



Scheme 2 Proposed mechanism for alkylation of indoles from enamide.

The production of bis-indolylmethanes in Table 4 might take place through the elimination of amine moiety of *N*-(1-(1*H*-indol-3-yl)ethyl)-*N*-methylacetamide **6a** with the assistance of iron catalyst to form the intermediate **III**, which undergoes a Friedel–Crafts-type process with indoles or indolizine to deliver the symmetrical or unsymmetrical bis-indolylmethanes (Scheme 3).[18a,21]



Scheme 3 Proposed mechanism for bis-indolylmethanes.

Conclusion

In summary, we have developed a highly efficient iron-catalyzed process for the addition of indoles to enamides under mild reaction conditions. The simple catalytic system worked well with a broad range of indoles and allowed the facile synthesis of alkylated indoles as well as symmetric and unsymmetric bis-indolylmethanes.

Experimental section

General

Unless otherwise stated, all reactions were carried out in an oven-dried flask in air. ^1H NMR spectra were recorded at 400 or 500 MHz and the chemical shifts are reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$ or DMSO-d_6. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; dt, doublet of triplet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were recorded at 100 or 125 MHz and referenced to the internal solvent signals (center peak is 77.00 ppm in $CDCl_3$ or 39.90 ppm in DMSO-d_6). Mass spectroscopy data were collected on an HRMS-EI instrument. Melting points were measured on a Yanaco MP-500 apparatus and uncorrected. FT-IR spectra were recorded on a Nicolet Nexus 470 FT-IR spectrophotometer and the data were reported in reciprocal centimetres (cm^{-1}). Indoles and enamide materials were purchased from common commercial sources and used without additional purification.

Representative procedure for the preparation of 3-alkylindole

To a mixture of indole (59 mg, 0.5 mmol), $FeCl_3$ (8 mg, 0.05 mmol) and CH_2Cl_2 (5 mL), 1-vinylpyrrolidin-2-one (67 mg, 0.6 mmol) was added dropwise at room temperature. The resulting mixture was stirred at 40 °C for 30 min. After the reaction, the reaction solution was filtered through a pad of celite, and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel, eluting with acetate–dichloromethane (1 : 10), provided the desired compound as a white solid (113 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.89 (s, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.19 (t, J = 7.2 Hz, 1 H), 7.13 (s, 1 H), 7.08 (t, J = 7.2 Hz, 1 H), 5.80 (q, J = 6.8 Hz, 1 H), 3.26 (dt, J = 8.6, 5.4 Hz, 1 H), 2.86 (dt, J = 9.0, 5.6 Hz, 1 H), 2.51–2.38 (m, 2 H), 1.95–1.85 (m, 1 H), 1.82–1.71 (m, 1 H), 1.58 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 136.6, 126.4, 122.3, 122.2, 119.7, 119.3, 115.7, 111.3, 42.7, 42.2, 31.8, 17.7, 16.7. HRMS (EI) Calcd for $C_{14}H_{16}N_2O$: $[M]^+$ 228.1263; Found, 228.1260; IR ν (KBr) 3244, 3058, 2973, 2932, 1659, 1493, 1455, 1428, 1342, 1287, 1248, 1198, 1116, 771, 745, 659. cm^{-1}; mp: 147–149 °C.

Representative procedure for the preparation of bis-indolylmethanes

N-Methyl-*N*-vinylacetamide (50 mg, 0.5 mmol), indole (176 mg, 1.5 mmol), $FeCl_3$ (8 mg, 0.05 mmol) and CH_2Cl_2 (5 mL) were introduced into the reaction vessel at room temperature. The resulting mixture was stirred at 40 °C for 1 h. After the reaction, the reaction solution was filtered through a pad of celite, and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel, eluting with acetate–petrol ether (1 : 10), provided the desired compound as a white solid (118 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.75 (s, 2 H), 7.63 (d, J = 7.2 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.22 (t, J = 7.4 Hz, 2 H), 7.10 (t, J = 7.6 Hz, 2 H), 6.84 (s, 2 H), 4.72 (q, J = 7.2 Hz, 1 H), 1.85 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 126.9, 121.8, 121.6, 121.3, 119.7, 119.0, 111.5, 28.2, 21.8.

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