Synthesis of Indolo[2,3-a]pyrrolo[3,4-c]carbazoles via the Oxidative Cyclization of Bisindolylmaleimides with $Pd(TFA)_2/Cu(OAc)_2$

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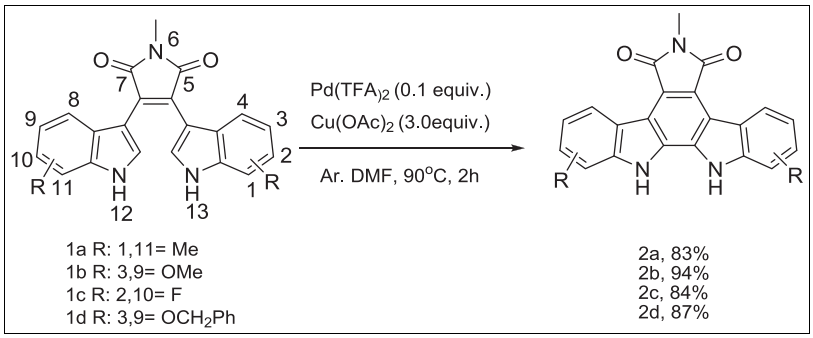

A new synthetic approach for the synthesis of indolo[2,3-a]pyrrolo[3,4-c]carbazoles based on the Cu^{2+}/Pd^{2+} catalytic system is described. The optimum condition is established via a systematic screening and utilized for the synthesis of four indolocarbazole aglycones with a satisfied yield.

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INTRODUCTION

The indolocarbazole alkaloids represent an interesting class of compounds that exhibit a wide range of biological activities [1]. The well-known members of this family are staurosporine [2], rebeccamycin [3] and K252a [4] with potent protein kinase C inhibitory [2b] and antitumor activities [4,5] (Fig. 1). The novel structures and significant biological activity have attracted intensive synthetic studies on these natural products and their structural analogues [6].

Several synthetic strategies have been reported for the synthesis of the indolocarbazole aglycone [7]. Among these methods, the most attractive one is the oxidation of the corresponding bisindolylmaleimides. The conversion of the bisindolylmaleimides to the indolocarbazoles has been explored by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[7a-b] iodine (with or without light),[7c-d] and phenyliodine bis(trifluoroacetate) (PIFA) [7e]. Furthermore, it was reported that indolocarbazoles could be synthesized from bisindolylmaleimides with the metallic catalysis system of $Pd(O_2CCF_3)_2$ [7f], $PdCl_2$ [7b], $Pd(OAc)_2$ [7g], $CuCl_2$ [7h], or $Pd(OAc)_2/CuCl_2$. [7i]

However, our synthetic efforts in constructing indolocarbazole skeleton from bisindolylmaleimide explored some disadvantages for the reported synthetic methods. For example, with iodine as the oxidant, the substrate concentration must be very dilute, and it was difficult to carry out the operation in a large scale. With DDQ as the oxidant, the product was difficult to isolate. The yields were very low when $CuCl_2$ was used as the oxidant. The Pd^{2+} mediated oxidative cyclization approach either required more than 2.5 equivalents of the palladium salt or did not work as well as reported. In this article, we report our systematic studies on a $Cu(OAc)_2/Pd(TFA)_2$ catalytic system to efficiently realize the construction of the indolocarbazole aglycone from the bisindolylmaleimides.

RESULTS AND DISCUSSION

Bisindolylmaleimides **1** were readily prepared by reaction of two equivalents of indolyllithium salts with 2,3-dibromomaleimide as reported [8]. Oxidative cyclization of bisindolylmaleimide under various reaction conditions was tested, and the results are summarized in Table 1.

All of the synthetic experiments were carried out under the protection of argon. With $Pd(TFA)_2$ (2.5 equiv.) as the catalyst and DMF as the solvent at 90°C for 4 hours, the reaction gave the desired product in 87% yield (entry **1**). When $Pd(TFA)_2$ was replaced with $PdCl_2$ (2.5 equiv.) or $Pd(OAc)_2$ (2.5 equiv.), the yields decreased sharply (entries **2** and **3**). The results showed that, of the three palladium catalysts, $Pd(TFA)_2$ was the best catalyst. In the case of $Pd(TFA)_2$ (0.1 equiv.) as the catalyst, some auxiliary oxidants were screened in order to reduce the amount of the palladium salt. The results showed that $Cu(OAc)_2$ was more efficient than $CuCl_2$ or $FeCl_3$ (entries **4–6**), which illustrated the importance of the matching of both the cations and the anions of the oxidant agents. The amount of the $Pd(TFA)_2$ catalyst and the variety of solvents were also screened in the presence of $Cu(OAc)_2$

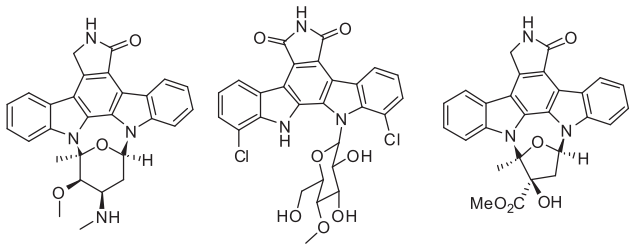


Figure 1. Structures of three indolocarbazole alkaloids.

(3.0 equiv.) at 90°C (entries **7–9**). The experimental results showed that with DMF as the solvent, the catalytic system of $Pd(TFA)_2$ (0.1 equiv.) and $Cu(OAc)_2$ (3.0 equiv.) gave the optimum results (entry **5**).

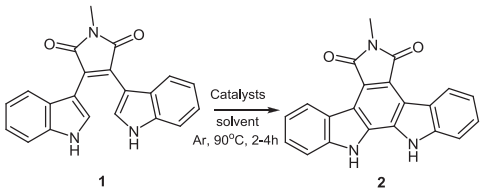
To further investigate the efficiency of the new catalytic system for the preparation of indolocarbazoles through the oxidative cyclization of bisindolylmaleimides, **1a-d** were tested under the optimum reaction conditions. The desired indolo[2,3-a]pyrrolo[3,4-c]carbazoles **2a-d** were obtained in 83–94% yields (Schemes 1 and 2).

A plausible Pd(0)/Pd(II) mechanism for the oxidative cyclization is outlined in Scheme 3. Most likely, the cyclization is initiated by an electrophilic Pd(II) species that is capable of inducing a cationic-driven ring closure, and the formed Pd(0) is oxidized back to Pd(II) by Cu (II) salts in the system to furnish the cycle.

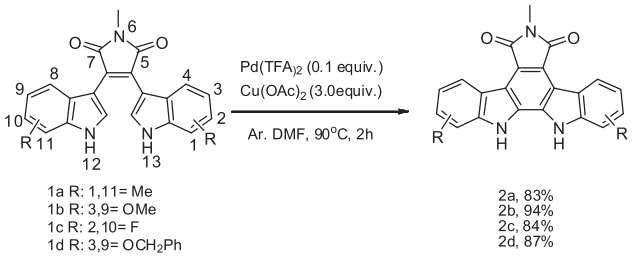
CONCLUSION

In conclusion, an efficient procedure was developed for the synthesis of pharmacologically important indolocarbazole aglycones and related analogues by the oxidative cyclization of bisindolylmaleimides with the $Cu(OAc)_2/Pd(TFA)_2$ catalytic system. Synthesis of indolocarbazole alkaloids and analogues with this method is ongoing in our laboratory.

Scheme 1. Synthesis of indolocarbazole from bisindolylmaleimides.



Scheme 2. Synthesis of indolocarbazole derivatives using the optimized Cu^{2+}/Pd^{2+} catalytic system.



Scheme 3. The possible mechanism of the Palladium-catalyzed cyclization of bisindolylmaleimides.

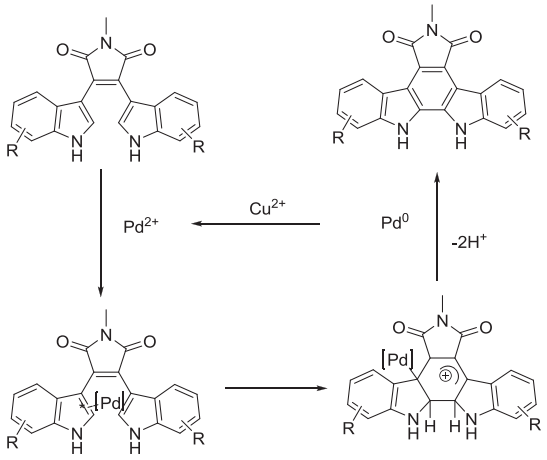


Table 1

Conditions and yields for the oxidative cyclization of bisindolylmaleimides.

Entry	Catalyst (equiv.)	Oxidant (equiv.)	Solvent	Time	Yield [%][a]
1	$Pd(TFA)_2$ (2.5)	—	DMF	4 h	87%
2	$PdCl_2$ (2.5)	—	DMF	4 h	25%
3	$Pd(OAc)_2$ (2.5)	—	DMF	4 h	34%
4	$Pd(TFA)_2$ (10%)	$CuCl_2$ (3.0)	DMF	4 h	20%
5	$Pd(TFA)_2$ (0.1)	$Cu(OAc)_2$ (3.0)	DMF	2 h	85%
6	$Pd(TFA)_2$ (0.1)	$FeCl_3$ (3.0)	DMF	4 h	minor
7	$Pd(TFA)_2$ (0.1)	$Cu(OAc)_2$ (3.0)	toluene	4 h	37%
8	$Pd(TFA)_2$ (0.1)	$Cu(OAc)_2$ (3.0)	THF	4 h	12%
9	$Pd(TFA)_2$ (0.05)	$Cu(OAc)_2$ (3.0)	DMF	3 h	72%
10	$Pd(TFA)_2$ (0.2)	$Cu(OAc)_2$ (3.0)	DMF	2 h	86%

[a]yields of isolated products.

EXPERIMENTAL

General. ^{1}H-NMR spectra were recorded at 600 or 300 MHz spectrometer at 24°C in the same solvent (DMSO-d_6) and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C-NMR spectra were recorded at 150 or 75 MHz spectrometer at 24°C in the same solvent (DMSO-d_6) and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. HRMS was carried out by Agilent LC/MSD TOF. All reagents were obtained from commercial suppliers unless otherwise stated.

General procedure. Under the protection of argon, a solution of bisindolylmaleimide **1a-d** (12.0 mmol), $Cu(OAc)_2$ (36.0 mmol), $Pd(TFA)_2$ (1.2 mmol) in DMF (100 mL) was heated at 120°C in a three-necked flask until TLC showed complete consumption of the bisindolylmaleimide. Thereafter, the reaction mixture was poured into aqueous HCl (0.2 M, 500 mL) and was extracted with EtOAc (3 × 100 mL). The organic phase was washed with aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL). Then, it was dried ($MgSO_4$), filtered through Celite, and concentrated. The residue was purified by column chromatography (silica gel; petroleum ether-EtOAc) to give indolocarbazole compounds 2a-d in yields of 83–94%.

12,13-Dihydro-1,11-dimethyl-6-methyl-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (2a). Yellow solid; yield 83%. mp: 105–107°C. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ ppm): 11.46(s, 2H), 8.77(d, 2H, J = 7.5 Hz), 7.36(d, 2H, J = 6.6 Hz), 7.26 (t, 2H, J = 7.2 Hz), 3.13(s, 3H), 2.67(s, 6H). ^{13}C-NMR (DMSO-d_6, 125 MHz, δ ppm): 169.84, 139.52, 128.72, 127.16, 121.80, 121.04, 120.49, 120.29, 118.88, 115.67, 23.49, 16.71. HRMS (EI): calcd 367.1321 for $C_{23}H_{17}N_3O_2$ $[M]^+$; found 367.1321.

12,13-Dihydro-3,9-dimethoxy-6-methyl-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (2b). Yellow solid; yield 94%. mp: 112–114°C. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ ppm): 11.54 (s, 2H), 8.54(d, 2H, J = 2.1 Hz), 7.68(d, 2H, J = 8.7 Hz), 7.16(dd, 2H, J = 8.7, 2.4 Hz), 3.90(s, 6H), 3.16(s, 3H). ^{13}C-NMR (DMSO-d_6, 125 MHz, δ ppm): 170.07, 153.86, 135.11, 129.47, 122.01, 118.56, 116.18, 115.40, 112.77, 106.14, 55.44, 23.54. HRMS (EI): calcd 399.1219 for $C_{23}H_{17}N_3O_4$ $[M]^+$; found 399.1216.

12,13-Dihydro-2,10-difluoro-6-methyl-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (2c). Yellow solid; yield 84%. mp: 123–125°C. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ ppm): 11.64 (s, 2H), 8.82(q, 2H, J = 5.7 Hz), 7.54(d, 2H), 7.13(t, 2H, J = 9.0 Hz), 3.02(s, 3H). ^{13}C-NMR (DMSO-d_6, 125 MHz, δ ppm): 171.08, 154.77, 136.01, 120.53, 123.11, 119.23, 117.11, 115.40, 113.07, 106.04, 23.64. HRMS (EI): calcd 375.0819 for $C_{21}H_{11}N_3O_2F_2$ $[M]^+$; found 375.0812.

12,13-Dihydro-3,9-dibenzyloxy-6-methyl-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (2d). Yellow solid; yield 87%. mp: 130–133°C. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ ppm): 11.54(s, 2H), 8.59(d, 2H, J = 2.1 Hz), 7.65(d, 2H, J = 8.7 Hz), 7.55(d, 4H, J = 7.2 Hz), 7.42(t, 4H, J = 6.9 Hz), 7.34(t, 2H, J = 7.2 Hz), 7.22(dd, 2H, J = 8.7, 2.4 Hz), 5.20 (s, 4H), 3.13(s, 3H). ^{13}C-NMR (DMSO-d_6, 125 MHz, δ ppm): 169.93, 152.78, 137.33, 135.22, 129.45, 128.36, 127.81, 127.74, 121.96, 118.52, 116.63, 115.31, 112.66, 107.69, 69.86, 23.51. HRMS (EI): calcd 551.1845 for $C_{35}H_{25}N_3O_4$ $[M]^+$; found 551.1840.

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