A Facile Synthesis of Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles via Oxidative Photocyclization of Bisindolylmaleimides

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Received 31 October 2002; revised 18 December 2002

Abstract: A simple and inexpensive oxidative photocyclization of the bisindolylmaleimides in the presence of a catalytic amount of iodine leading to indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles in 84–90% yields is described.

Key words: photooxidation, indole alkaloid, heterocycle, staurosporine, aglycon

The indolocarbazole alkaloids are structurally rare, but biologically very interesting class of natural products.[1] The most well known members of this family are rebeccamycin **1**[2], staurosporine **2**,[3] and K252a **3**[4] owing to their wide range of pharmacological activities such as antimicrobial,[5] hypotensive,[6] cell cytotoxic,[3a] inhibition of protein kinase C[3a] and platelet aggregation.[7] Their unique structures coupled with their wide range of biological activities have recently attracted intensive synthetic studies on these molecules[8–10] and their aglycon.[11]

The indolocarbazole, the common aglycon moiety of these compounds, is known to retain much of the activity of the parent molecule. Several methods have been reported for the synthesis of aglycons **4** and **5**. Among them, the approach involving oxidative cyclization of bisindolylmaleimide **6** is the most attractive because it is short and the starting materials are readily available. Various oxidizing agents, such as DDQ (with or without *p*-TsOH),[11g–i] $Pd(OAc)_2$,[11j] $PdCl_2$, $Pd(O_2CCF_3)_2$[11f] and PIFA/$BF_3{\cdot}OEt_2$[11c] have been previously employed in this oxidative cyclization. However, most of these reagents have their own limitations, for example a) with DDQ/*p*-TsOH used as an oxidant, it is difficult to remove DDQ by-products, b) reactions with Pd are stoichiometric, expensive, and further, removal of Pd from indolocarbazoles is difficult (due to poor solubility), c) the yields are low with PIFA/$BF_3{\cdot}OEt_2$. An alternate method is an oxidative photocyclization. Earlier, a couple of photocyclizations of indolocarbazole lactams were reported[12] to provide the staurosporine aglycon moiety in 37% and 65% yields, respectively. Danishefsky and co-workers[9c] have disclosed the photocyclization of indole glycoside derivative using Hanvonia medium pressure Hg lamp 450 W with Vycor filter in the presence of a catalytic amount of iodine while air was bubbled into the benzene solution for 8 hours. The corresponding indolocarbazole glycoside was obtained in 73% yield. Recently Slater and co-workers[11e] have ac-

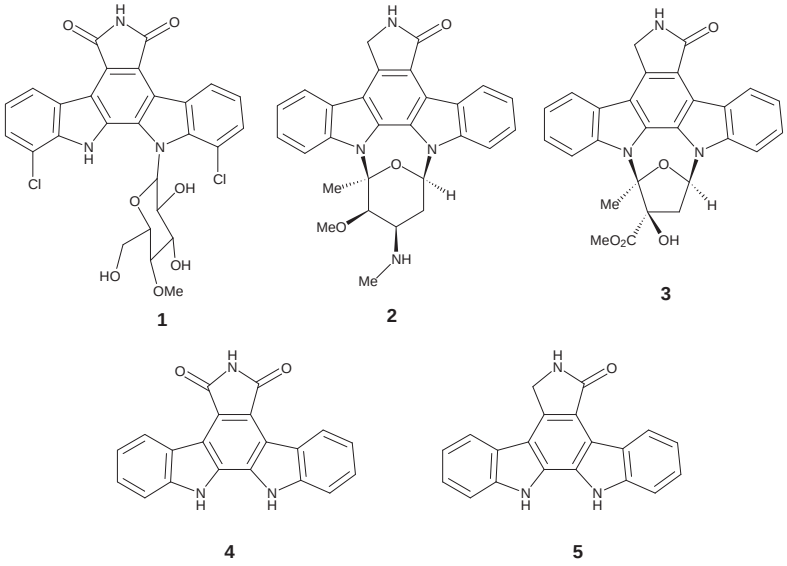
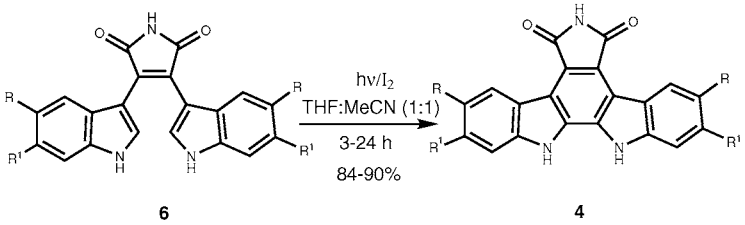


Figure 1

Synthesis 2003, No. 4, Print: 18 03 2003.
Art Id.1437-210X,E;2003,0,04,0497,0500,ftx,en;F08902SS.pdf.

ISSN 0039-7881



Scheme 1

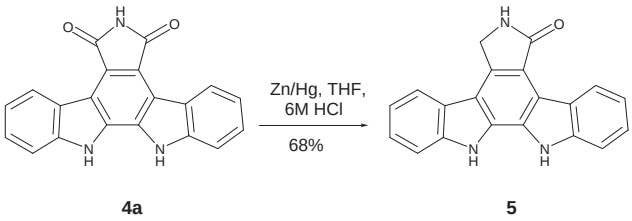
complished a similar photocyclization in isopropanol using excess of iodine in an inert atmosphere to provide the product in 72% yield.

As part of our ongoing research program towards the total synthesis of staurosporine[13] and K252a, herein we report an improved and practical procedure for the synthesis of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole ring system (**4**).

Table 1 Oxidative Photocyclization of Indolylmaleimides **6a**–**e**

Entry	R	R^1	Time (h)	Product	Yield (%)
1	H	H	12	**4a**	85
2	F	H	6	**4b**	90
3	Br	H	3	**4c**	90
4	OCH_3	H	24	**4d**	84
5	H	Cl	6	**4e**	87

A series of bisindolylmaleimides **6a**–**e** were readily obtained by the reaction of appropriately substituted indolylmagnesium bromide with 3,4-dichloromaleimides.[14] Oxidative cyclization of **6a**–**e** using an ordinary 400 W mercury lamp in the presence of a catalytic amount of iodine in THF–CH_3CN (1:1) at room temperature furnished the desired indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **4a**–**e** in 84–90% yields (Scheme 1, Table 1). It is noteworthy that, even without protection of imide N–H or indolo N–H, the reaction still gives good yields. The presence of an electron-withdrawing group in the substrate **6** enhances the reactivity (entries 2, 3, and 5) while the reaction was slow when an electron donating substituent was present in **6** (entry 4). This high-yielding photocyclization process can be successfully scaled up to multigram level. In addition, the chemical yield of the reaction is independent on the substrate concentration over a range of 0.004–0.015 M. However, at concentration higher than 0.015 M the reaction could not reach completion owing to the precipitation of the product, which blocked light for the photocyclization. The reduction of symmetric imide **4a** to the staurosporinone **5** was achieved by slightly modifying the Clemmenson reduction method. Thus, zinc amalgam prepared from zinc powder was washed with dilute hydrochloric acid and used in the reduction of **4a** in a mixture of 6 N HCl and THF under refluxing conditions for 1.5 hours to afford the lactam **5** in 68% yield. Most of the reported methods that converted **4** to **5** have conducted in a three-step procedure involving the initial protection of imide nitrogen and subsequent Clemmensen reduction and deprotection.[10c,11i,15] Although there exist two reports[16] describing a one-step conversion of **4** to **5** by Clemmensen reduction, the lactam is obtained in a relatively better yield in the present case.



Scheme 2

In conclusion, a simple and practical procedure was developed for the synthesis of pharmacologically important rebeccamycin, staurosporine, and K252a aglycons and their analogues by the photooxidation of bisindolylmaleimides using an ordinary Hg lamp. The method is operationally simple, obviating the need for oxygen bubbling and expensive equipment.

Oxidative Photocyclization of 6; Typical Procedure

Indolylmaleimide (**6a**, 0.150 g, 0.45 mmol) was dissolved in THF–CH_3CN (1:1, 100 mL) and catalytic amount of I_2 (0.010 g) was added. The reaction mixture was irradiated at r.t. using two 400 W mercury lamps (Eye lighting Co., LTD, Taiwan, Model-H 400, high pressure, 560 nm) for 12 h. The solvent was removed in vacuo, the residue was dissolved in THF (3 mL) and reprecipitated with hexane. The solid was filtered, dried at 150 °C under vacuum and was characterized as **4a**[11e] (0.127 g, 85%). On a 5.0 g scale at 0.015 M concentration, the reaction was completed in 96 h under similar reaction conditions and the desired product was obtained in 86% yield; mp > 350 °C.

IR (KBr): 3354, 3216, 1722, 1681 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.71 (s, 2 H, indole NH), 10.96 (s, 1 H, imide NH), 8.97 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6) δ = 171.3, 140.3, 129.0, 126.7, 124.3, 121.6, 120.2, 119.9, 115.5, 112.0.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{11}N_3O_2$, 325.0850; found, 325.0854.

12,13-Dihydro-3,9-difluoro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)-dione (4b)[17]
Mp > 350 °C.

IR (KBr) 3364, 3199, 1746, 1699 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 11.80 (s, 2 H, indole NH), 11.04 (s, 1 H, imide NH), 8.62 (dd, *J* = 2.5, 10.0 Hz, 2 H), 7.81 (dd, *J* = 4.5, 9.0 Hz, 2 H), 7.40 (ddd, *J* = 2.5, 9.0, 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.2, 157.8, 155.9, 136.7, 130.0, 121.8, 121.7, 120.0, 115.2, 115.1, 114.8, 114.6, 113.4, 113.3, 109.1, 108.9.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_9F_2N_3O_2$, 361.0663; found, 361.0667.

12,13-Dihydro-3,9-dibromo-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)-dione (4c)[11e]
Mp > 350 °C.

IR (KBr) 3364, 3199, 1738, 1699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.59 (s, 2 H, indole NH), 10.93 (s, 1 H, imide NH), 8.86 (s, 2 H), 7.60 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.9, 138.7, 129.0, 126.1, 123.0, 120.0, 114.3, 113.8, 112.2.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_9Br_2N_3O_2$, 480.9001; found, 480.8990.

12,13-Dihydro-3,9-dimethoxy-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-(6*H*)-dione (4d)[11e]
Mp > 350 °C.

IR (KBr): 3333, 3245, 1746, 1713 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.52 (s, 2 H, indole NH), 10.92 (s, 1 H, imide NH), 8.54 (s, 2 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 153.8, 135.0, 129.6, 122.1, 119.6, 116.0, 115.3, 112.7, 106.6, 55.5.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{22}H_{15}N_3O_4$, 385.1063; found, 385.1056.

12,13-Dihydro-2,10-dichloro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)-dione (4e)
Mp > 350 °C.

IR (KBr) 3390, 3221, 1738, 1698 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.61 (s, 2 H, indole NH), 10.93 (s, 1 H, imide NH), 8.75 (d, *J* = 8.4 Hz, 2 H), 7.76 (s, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.0, 140.8, 131.3, 129.2, 125.4, 120.5, 120.3, 120.0, 115.0, 111.9.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_9Cl_2N_3O_2$, 393.0272; found, 393.0269.

Preparation of Staurosporinone 5
To a solution of indolocarbazole (**4a**, 0.100 g, 0.3 mmol) in THF (20 mL) was added zinc amalgam (2 g) and the reaction mixture was heated under reflux. As the refluxing commenced, 6 N HCl (2.5 mL) was added dropwise over a period of 30 min. After the addition, heating was continued for an additional 1 h and then diluted with EtOAc (25 mL). The inorganic solid was filtered off and the filtrate was washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to flash chromatography eluting with EtOAc–hexanes (3:1) to furnish **5**[18] in 68% yield (0.065 g,); mp > 350 °C.

IR (KBr): 3435, 3304, 1647 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.48 (s, 1 H, NH), 11.31 (s, 1 H, NH), 9.20 (d, *J* = 8.0 Hz, 1 H), 8.47 (s, 1 H, lactam NH), 8.02 (d, *J* = 7.5 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H,), 7.70 (d, *J* = 7.5 Hz, 1 H), 7.47 (dd, *J* = 7.5, 8.0 Hz, 1 H), 7.43 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.28 (dd, *J* = 7.0, 7.5 Hz, 1 H), 7.21 (dd, *J* = 7.0, 8.0 Hz, 1 H), 4.95 (s, 2 H, lactam CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.5, 139.2, 139.1, 132.9, 127.9, 125.4, 125.2, 125.0, 122.8, 122.6, 121.1, 119.9, 119.0, 118.9, 115.6, 114.2, 111.9, 111.4, 45.3.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_{13}N_3O$, 311.1059; found, 311.1021.

Acknowledgment

We thank the National Science Council, Republic of China for the financial support.

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