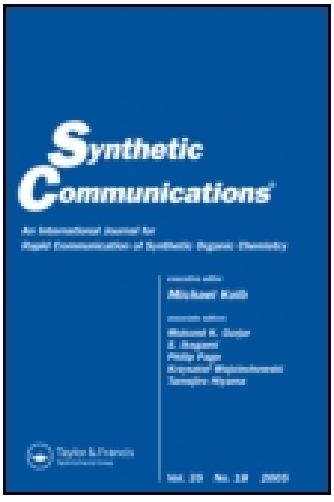

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Synthesis of a Novel N-Nitroalkyl Bisindolylmaleimide

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Synthesis of a Novel *N*-Nitroalkyl Bisindolylmaleimide

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Abstract: We describe the synthesis of the novel *N*-nitropropyl bisindolylmaleimide **6.**

Keywords: bisindolylmaleimides, indoles, nitroalkyl group

The natural bisindolylmaleimide arcyriarubin A (**1**) is a highly selective, potent protein kinase C (PKC) inhibitor ($IC_{50} = 87$ nM).[1] Many synthetic analogues of **1** have been prepared, among which GF109203x (**2**), Ro 31–7549 (**3**), Gö6983 (**4**), and Ro 31–8220 (**5**) exhibit strong pharmacological activities (Fig. 1).[2] In our search for novel checkpoint kinase 1 inhibitors, we have previously synthesized several bisindolylmaleimides and the corresponding indolocarbazoles.[3] During these studies, we found that no synthesis of *N*-nitroalkyl-substituted bisindolylmaleimides had been reported. The nitroalkyl group possesses further challenges because of the high acidity of the α-hydrogen. Herein, we report the synthesis of the novel nitropropyl-substituted bisindolylmaleimide **6**.

To synthesize **6**, we initially adopted a protecting group strategy in which the phenylsulfonyl protecting group was removed after the base-mediated coupling reaction to furnish the known anhydride **11** (Scheme 1).[1a] An attempt to prepare 1-phenylsulfonylindole-3-glyoxyloyl chloride from

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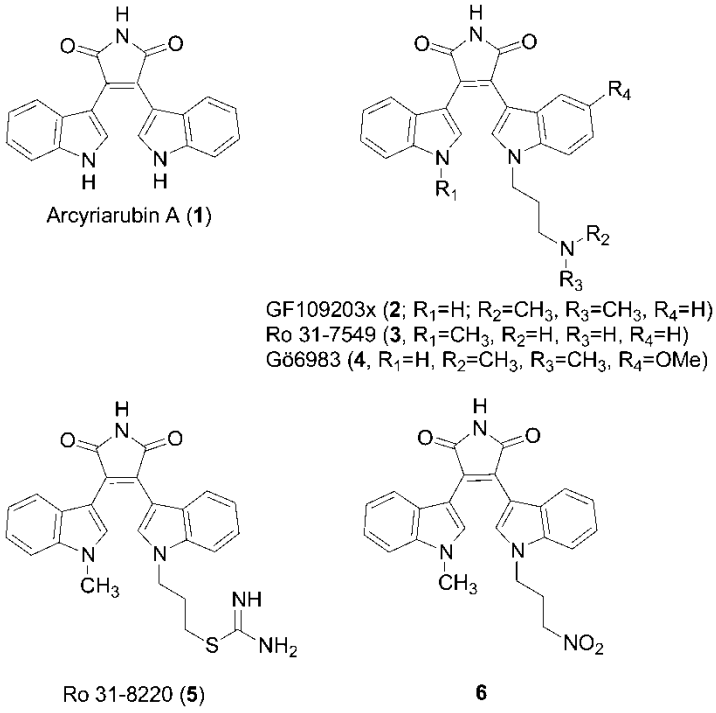
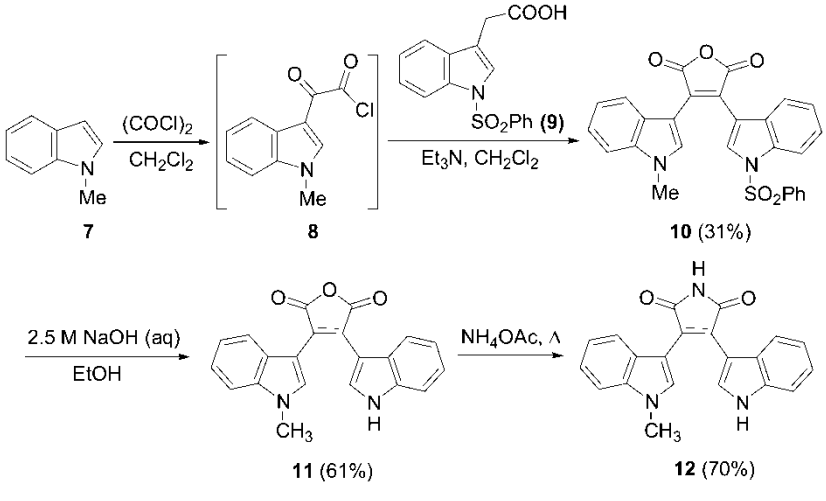


Figure 1. Arcyriarubin A and its synthetic analogues.

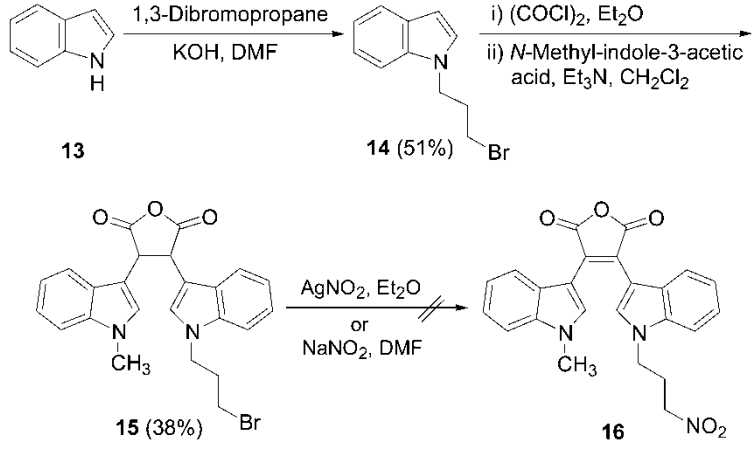


Scheme 1.

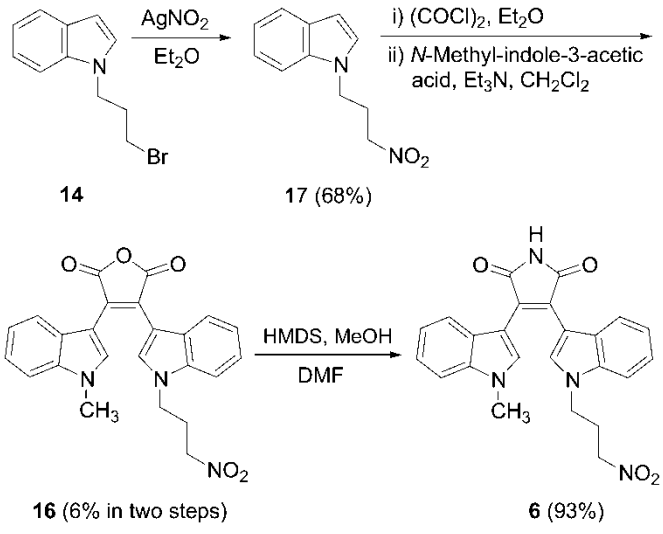
1-phenylsulfonylindole by the treatment of oxalyl chloride was unsuccessful (even with a longer reaction time) because of the strong electron-withdrawing effect of the phenylsulfonyl group. 1-(Phenylsulfonyl)indole-3-acetic acid (**9**), required for the coupling reaction, was prepared from indole-3-acetic acid using benzenesulfonyl chloride in the presence of excess (2.1 equiv) *n*-butyllithium at −70°C. The anhydride **11** was converted to known imide **12** by heating with ammonium acetate,[4] but an attempt to alkylate the indole nitrogen of **12** with 1,3-dibromopropane furnished a complex mixture of products.

Therefore, we alkylated indole with 1,3-dibromopropane to furnish 3-bromopropylindole (**14**),[5] which was subjected to the coupling reaction to give the desired anhydride **15** in 38% yield (Scheme 2). However, attempts to convert bromo derivative **15** to nitro compound **16** with silver nitrite or sodium nitrite did not furnish the product or gave undesired products that could not be identified. Also, we were unsuccessful in converting the anhydride **15** to the corresponding imide using 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and methanol.[6]

Therefore, we performed the bromo to nitro conversion at the early stage of the synthesis (Scheme 3),[5] and the resulting nitro derivative **17** was subjected to the coupling reaction. To our satisfaction, the desired anhydride **16** was prepared, albeit in very low yield perhaps due to the acidic hydrogens α- to the nitro group. The anhydride **16** was finally converted to the target molecule **6** in 93% yield. An attempt to alkylate indole with 1-chloro-3-nitropropane, prepared from 1-bromo-3-chloropropane,[7] in the presence of sodium hydride unexpectedly furnished a small amount of indole-1-propionitrile *N*-oxide (**18**).



Scheme 2.



Scheme 3.

EXPERIMENTAL

Melting points were determined with a Mel-Temp laboratory device apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 600 series FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian XL-300 or 500 Fourier transform NMR spectrometer. Both low- and high-resolution mass spectra were carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana Champaign. Anhydrous THF and CH_2Cl_2 were prepared by a solvent purification system. All other solvents (analytical grade), including anhydrous solvents and reagents, were used as received.

1-(Phenylsulfonyl)indole-3-acetic Acid (9)

To a stirred solution of indole-3-acetic acid (2.63 g, 15 mmol) in THF (80 ml) at $-70^{\circ}C$, 2.5 M *n*-BuLi in hexane (12.8 mL, 32 mmol) was added dropwise. The mixture was stirred at the same temperature for 1 h. A solution of benzenesulfonyl chloride (1.9 mL, 15 mmol) in THF (25 mL) was added very slowly to the reaction mixture at $-70^{\circ}C$. The mixture was allowed to come to rt and stirred for 16 h. The solvent was removed in vacuo, and the residue was redissolved in dichloromethane and washed with 1 N HCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was recrystallized from ethyl acetate–hexanes to furnish the desired product (3.31 g, 70%) as a brownish solid: mp 171–173°C (dec); IR (thin

film) 1710, 1447, 1366, 1174, 1121, 746 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.98–7.93 (m, 3H), 7.75–7.54 (m, 5H), 7.38–7.24 (m, 2H), 3.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 171.9, 137.1, 134.6, 134.3, 130.5, 129.9, 126.6, 124.9, 123.3, 120.3, 116.6, 113.1, 30.2; LRMS (EI) m/z 315 (M^+, 100%), 270, 132, 77; HRMS (EI) calcd. for $C_{16}H_{13}NO_4S$: 315.0565; found: 315.0560.

3-[1-(3-Bromo-propyl)-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-3-yl)-furan-2,5-dione (15)

To a stirred solution of 1-(3-bromopropyl)indole (0.71 g, 3 mmol) in anhydrous ether (30 mL) at 0°C, oxalyl chloride (0.43 mg, 3.3 mmol) was added dropwise. The mixture was stirred at 0°C for 30 min. The solvent was evaporated, and the crude residue was redissolved in dichloromethane (30 mL) and added to a solution of *N*-methylindole-3-acetic acid (0.57 mg, 3 mmol) and triethylamine (0.61 mg, 6 mmol) in dichloromethane (12 mL) over 1 h. The mixture was stirred for 20 h. The crude product was purified by column chromatography on silica gel (dichloromethane–methanol = 99:1) to yield the desired product (0.53 mg, 38%) as a red solid: mp 169–171°C; IR (thin film) 1815, 1749, 1628, 1529, 1254, 1226, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.00 (s, 1H), 7.79 (s, 1H), 7.56 (d, 1H, $J = 8.5$ Hz), 7.48 (d, 1H, $J = 8.2$ Hz), 7.08–7.14 (m, 2H), 7.04 (d, 1H, $J = 7.9$ Hz), 6.82 (t, 1H, $J = 7.9$ Hz), 6.65–6.71 (m, 2H), 4.35 (t, 2H, $J = 6.6$ Hz), 3.89 (s, 3H), 3.38 (t, 2H, $J = 6.6$ Hz), 2.24 (qn, 2H, $J = 6.6$ Hz); ^{13}C NMR (DMSO-d_6) δ 166.5, 166.3, 136.8, 135.8, 134.5, 132.7, 128.4, 126.8, 125.7, 124.9, 122.4, 122.3, 121.5, 121.4, 120.2, 120.1, 110.6, 110.4, 104.7, 103.9, 44.3, 33.1, 32.7, 31.2; LRMS (EI) m/z 463 (M^+), 418, 390, 382, 279, 269, 167, 149 (100%); HRMS (EI) calcd. for $C_{24}H_{19}BrN_2O_3$: 462.0579; found: 462.0587.

1-(3-Nitropropyl)indole (17)

A mixture of 1-(3-bromopropyl)indole (1.15 g, 4.8 mmol) and silver nitrite (2.60 g, 16.8 mmol) in ether (50 mL) was stirred in dark for 2 d. The mixture was filtered through a sintered-glass funnel and washed with ether. The filtrate was concentrated (at 0°C with icecooling) in rotovap to about 15–20 mL. The crude liquid was subjected to column chromatography on silica gel (pet. ether–ether = 2:1) to furnish the desired product (0.66 g, 68%) as a colorless liquid. 1-(3-Nitropropyl)indole is stable in etheral solution but slowly decomposes in the dry state even at 0–4°C. IR (thin film) 1551, 1462, 1314, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d, 1H, $J = 7.8$ Hz), 7.27–7.37 (m, 2H), 7.17–7.23 (m, 1H), 7.10 (d, 1H, $J = 3.2$ Hz), 6.58 (dd, 1H, $J = 3.2$ Hz, 0.7 Hz), 4.24–4.30 (m, 4H), 2.49

(qn, 2H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 135.8, 128.9, 127.9, 122.1, 121.4, 119.9, 109.1, 102.2, 72.3, 42.8, 27.7.

3-(1-Methyl-1*H*-indol-3-yl)-4-[1-(3-nitro-propyl)-1*H*-indol-3-yl]-furan-2,5-dione (16)

To a stirred solution of 1-(3-nitropropyl)indole (0.61 mg, 3 mmol) in anhydrous ether (30 mL) at 0°C, oxalyl chloride (0.43 g, 3.3 mmol) was added dropwise. The mixture was stirred at 0°C for 1.5 h. Then solvent was evaporated; the residue was redissolved in dichloromethane (30 mL) and added dropwise (throughout 1 h) to a stirred solution of *N*-methylindole-3-acetic acid (0.57 g, 3 mmol) and triethylamine (0.61 g, 6 mmol) in dichloromethane (12 mL). The mixture was stirred for 23 h. The crude residue was purified by column chromatography on silica gel (dichloromethane–methanol = 97:3) to yield the desired product (74 mg, 6%) as a red solid: IR (thin film) 1751, 1612, 1552, 1529, 1467, 1255, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.00 (s, 1H), 7.83 (s, 1H), 7.56 (d, 1H, $J = 8.1$ Hz), 7.49 (d, 1H, $J = 8.1$ Hz), 7.08–7.15 (m, 2H), 7.02 (d, 1H, $J = 8.1$ Hz), 6.81 (t, 1H, $J = 7.6$ Hz), 6.68–6.73 (m, 2H), 4.52 (t, 2H, $J = 6.8$ Hz), 4.35 (t, 2H, $J = 7.1$ Hz), 3.89 (s, 3H), 2.35 (qn, 2H, $J = 6.8$ Hz); LRMS (ESI) m/z 430 [$M^+ + H$], 282 (100%); HRMS (ESI) calcd. for $C_{24}H_{20}N_3O_5$: 430.1403 [M + H]; found: 430.1401.

3-(1-Methyl-1*H*-indol-3-yl)-4-[1-(3-nitro-propyl)-1*H*-indol-3-yl]-pyrrole-2,5-dione (6)

To a solution of anhydride **16** (35 mg, 0.08 mmol) in DMF (1 mL) at rt, HMDS (132 mg, 0.8 mmol) and methanol (13 mg, 0.4 mmol) were quickly added. The flask was tightly sealed, and the mixture was stirred for 24 h. It was poured into water (25 mL) and extracted with ethyl acetate (2 × 25 mL) and dried (Na_2SO_4). The crude residue was purified by column chromatography (dichloromethane–methanol = 95:5) to yield the desired product (32 mg, 93%) as a red solid: mp 125–127°C; IR (thin film) 1703, 1609, 1551, 1467, 1334, 744 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H), 7.87 (s, 1H), 7.70 (s, 1H), 7.48 (d, 1H, $J = 8.2$ Hz), 7.41 (d, 1H, $J = 8.2$ Hz), 7.00–7.08 (m, 2H), 6.94 (d, 1H, $J = 7.9$ Hz), 6.73 (t, 1H, $J = 7.9$ Hz), 6.61–6.65 (m, 2H), 4.49 (t, 2H, $J = 6.9$ Hz), 4.32 (t, 2H, $J = 6.9$ Hz), 3.86 (s, 3H), 2.34 (qn, 2H, $J = 6.9$ Hz); ^{13}C NMR (DMSO-d_6) δ 173.0, 172.9, 136.6, 135.6, 133.3, 131.6, 128.1, 126.5, 126.2, 125.5, 122.0, 121.8, 121.4, 121.1, 119.8, 119.6, 110.2, 110.0, 105.6, 104.5, 72.6, 42.7, 33.0, 27.2; LRMS (ESI) m/z 451 [$M^+ + Na$], 429 [$M^+ + H$]; HRMS (ESI) calcd. for $C_{24}H_{21}N_4O_4$: 429.1563 [M + H]; found 429.1544.

3-[2,5-Dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-3-furanyl]-1-(phenylsulfonyl)-1*H*-indole (10): mp > 200°C (dec); ^{1}H-NMR (acetone-d_6) δ 8.12 (m, 2H), 8.08–8.00 (m, 2H), 7.81–7.76 (m, 1H), 7.68–7.63 (m, 2H), 7.41 (d, 1H, $J = 8.3$ Hz), 7.26–7.21 (m, 1H), 7.06–7.01 (m, 2H), 6.90–6.85 (m, 1H), 6.47 (d, 1H, $J = 8.1$ Hz), 6.31–6.26 (m, 1H), 3.96 (s, 3H); ^{13}C-NMR (acetone-d_6) δ 167.1, 166.7, 138.5, 138.3, 136.7, 135.7, 135.2, 135.1, 130.9, 129.8, 129.5, 128.0, 126.4, 126.2, 124.3, 123.6, 122.9, 122.1, 121.8, 114.3, 113.5, 111.4, 110.7, 105.3, 33.9.

3-(1*H*-Indol-3-yl)-4-(1-methyl-1*H*-indol-3-yl)-2,5-furandione (11): mp 246–248°C; IR (thin film): 3371, 1818, 1742, 1528, 1247, 113, 740 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 11.06 (brs, 1H), 7.94 (s, 1H), 7.90 (s, 1H), 7.46 (t, 2H, $J = 8.9$ Hz), 7.10 (dt, 1H, $J = 7.6$ Hz, 0.9 Hz), 7.05 (dt, 1H, $J = 7.6$ Hz, 0.9 Hz), 6.96 (d, 1H, $J = 8.2$ Hz), 6.91 (d, 1H, $J = 7.9$ Hz), 6.71 (t, 2H, $J = 7.6$ Hz), 3.95 (s, 3H); ^{13}C-NMR (acetone-d_6) δ 167.7, 167.6, 138.1, 135.1, 131.1, 131.0, 129.2, 128.8, 126.9, 123.3, 123.2, 122.8, 122.5, 121.1, 120.9, 112.8, 112.7, 111.0, 106.8, 105.7, 33.6; LRMS (EI) m/z 342 (M^+, 100%), 270, 255, 227, 135, 121, 114; HRMS (El) calcd for $C_{21}H_{14}N_2O_3$: 342.100; found: 342.1003.

1-(3-Bromopropyl)indole (14): ^{1}H-NMR ($CDCl_3$) δ 7.71-7.73 (m, 1H), 7.45 (d, 1H, $J = 8.3$ Hz), 7.29–7.32 (m, 1H), 7.19–7.22 (m, 2H), 6.58 (d, 1H, $J = 2.9$ Hz), 4.38 (t, 2H, $J = 6.3$ Hz), 3.35 (t, 2H, $J = 6.3$ Hz), 2.39 (2H, qn, $J = 6.3$ Hz); ^{13}C-NMR ($CDCl_3$) δ 135.9, 128.8, 128.1, 121.8, 121.2, 119.6, 109.4, 101.6, 44.0, 32.8, 30.7.

Indole-1-propionitrile-*N*-oxide (18): ^{1}H-NMR ($CDCl_3$) δ 8.29 (d, 1H, $J = 8.3$ Hz), 7.64 (d, 1H, $J = 7.8$ Hz), 7.38 (dt, 1H, $J = 7.7$ Hz, 0.7 Hz), 7.28 (dt, 1H, $J = 7.4$ Hz, 1.0 Hz), 7.10–7.12 (m, 1H), 4.47–4.52 (m, 2H), 3.46 (q, 2H, $J = 9.7$ Hz); ^{13}C-NMR ($CDCl_3$) δ 154.2, 135.1, 130.1, 125.5, 124.2, 122.5, 121.1, 115.4, 106.9, 106.8, 68.5, 35.0; LRMS (El) m/z 186 (M^+, 100%) 117: HRMS (EI) calcd for $C_{11}H_{10}N_2O$: 186.0793, found 186.0799.

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