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Unexpected Formation of the Arcyriacyanin System by Condensation of a 3-Bromo-4-(indol-3-yl)maleimide with (2-Nitrophenyl)acetates*

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The reaction of an *N*-protected 3-bromo-4-(indol-3-yl)maleimide with methyl (2-nitrophenyl)acetates in the presence of base affords condensed cycloheptatriene derivatives which can be transformed into arcyriacyanin-type alkaloids. The unusual reaction sequence implies a heptatrienyl–cycloheptadienyl anion rearrangement followed by a 1,5-sigmatropic shift to yield the thermodynamically more stable cycloheptatriene derivative.

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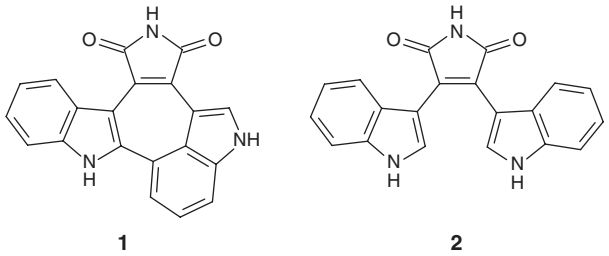
The slime mould alkaloid arcyriacyanin A **1**[1] (Scheme 1) is a member of the bisindolylmaleimide group of alkaloids[2] that includes protein kinase inhibitors like staurosporine and arcyriarubin A **2**. Arcyriacyanin A **1** shows unique antitumour properties, and inhibits protein kinase C and protein tyrosine kinase.[3] We and others have developed syntheses for arcyriacyanin A based on palladium-catalyzed reactions.[1c,3,4] In this communication we report on a highly convergent method of attaining the arcyriacyanin system through cyclization of suitable nitrophenyl precursors.



1 **2**

Scheme 1.

Our strategy is based on the unexpected discovery that reaction of *N*-protected 3-bromo-4-(indol-3-yl)maleimide **3**[5] with the anion of methyl (2-nitrophenyl)acetate **4**[6] at −78°C and warming to room temperature affords the yellow benzo[6,7]pyrrolo[3′,4′:3,4]cyclohepta[1,2-*b*]indole **6** in 40% yield (Scheme 2). No trace of the expected substitution product **5** could be detected. The structure of compound **6** was established through extensive NMR studies (see Experimental) and confirmed by a single crystal X-ray analysis (Fig. 1).[7] Upon thermolysis,[8] the Boc group can be easily removed to yield the free indole **7**, which is a close structural analogue of arcyriacyanin **1**.

In order to study the mechanism of the ring closure, we followed the reaction between components **3** and **4** at lower temperatures. When the reaction is carried out at −78°C and monitored by TLC, the rapid formation of a new product can be detected. Upon raising the temperature to −60°C the initial compound is transformed into a second product, which has a characteristic green fluorescence under UV light, and this then yields the final product **6** at temperatures above −30°C. The primary product could be isolated by quenching the reaction with aqueous citric acid at −78°C, and subsequent chromatography on silica gel yielded the pure compound in approximately 50% yield. Its spectroscopic data were in agreement with those expected for maleimide **5**. Upon treatment with a mild base, compound **5** could be converted into **6** in approximately 80% yield. A second intermediate was obtained in pure form upon treatment of **5** with lithium iodide in DMF followed by rapid chromatography of the crude product on a pre-cooled silica-gel column. Immediate NMR measurements ($CDCl_3$) at −50°C established that this intermediate had structure **10**. In particular, at −50°C, signals for a 3 : 1 mixture of the (*E*)- and (*Z*)-diastereomers of **10** are observed; this indicates a hindered rotation of the Boc residue. The doubling-up of signals due to H8, H8b, H10, and the Boc protons disappears upon warming the NMR sample to room temperature. Concurrently, signals for the thermodynamically more stable cycloheptatriene isomer **6** gradually emerge, and rearrangement is complete within 30 minutes.

From these results we suggest that the reaction proceeds through the pathway depicted in Scheme 3. Thus, anion **8**, derived from the primary product **5**, undergoes an electrocyclic heptatrienyl–cycloheptadienyl anion rearrangement[9]

* Dedicated to Professor Lewis Mander on the occasion of his 65th birthday.

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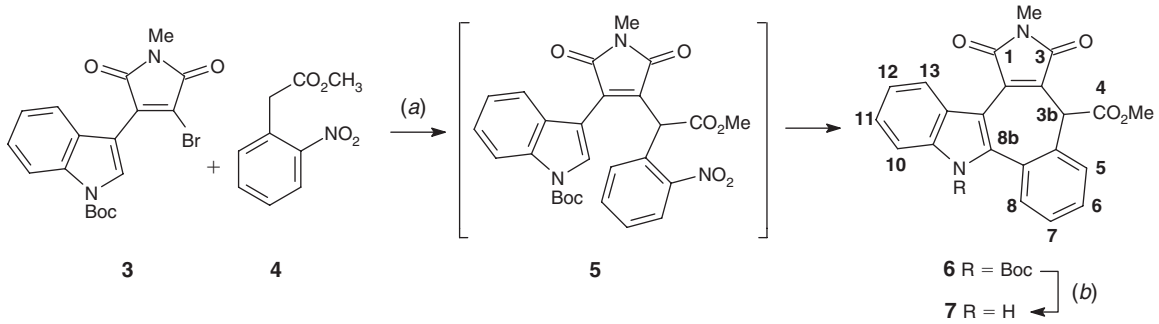
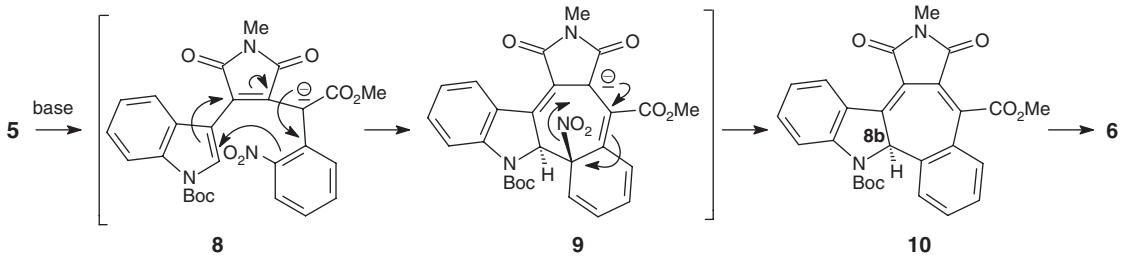
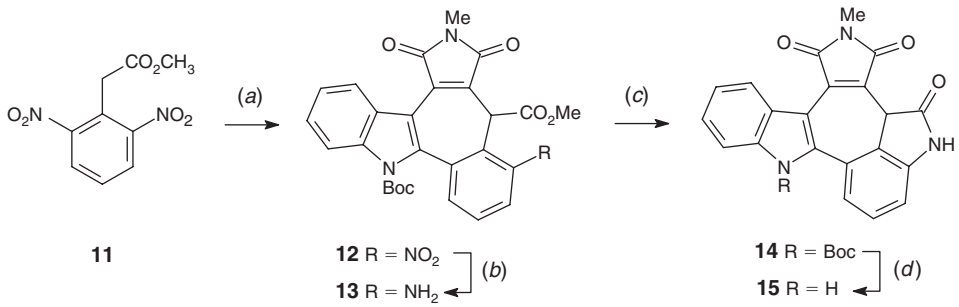


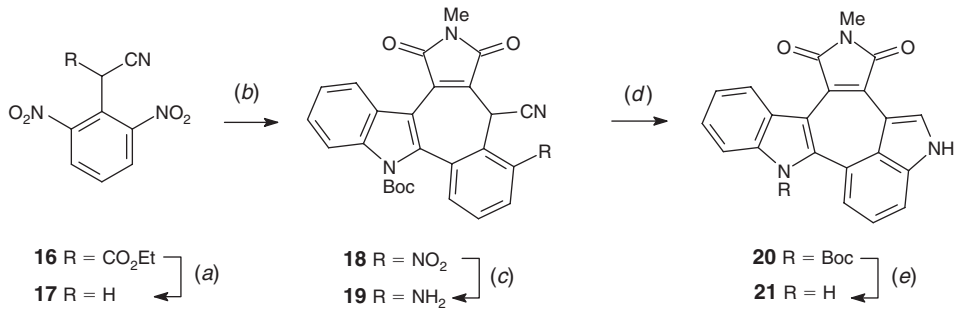
Scheme 2. Reagents and conditions: (*a*) **4**, NaH, THF, room temp.; then −78°C, **3**, and warming to room temp., 36 h; then aqueous citric acid; and (*b*) 180°C, 10 min.



Scheme 3. Base-induced cyclization of the primary substituted product **5**.



Scheme 4. Reagents and conditions: (*a*) KH, [18]crown-6, THF, **11**, 0°C, 2 h; then **3**, THF, 0°C to room temp., NEt_3, 30 h; (*b*) 10% Pd/C, H_2, EtOAc, 3 bar, room temp., 3 h; (*c*) 0.2 equiv. $(HOBu_2SnOSnBu_2SCN)_2$,[12] benzene, 80°C, 36 h; and (*d*) 180°C, 5 min.



Scheme 5. Reagents and conditions: (*a*) BHT, 2 N HCl (cat.), DMSO, heat until the red solution turns brown; then ice water; (*b*) KH, [18]crown-6, **17**, THF, −78°C; then **3**, THF, NEt_3, −78°C to room temp., 15 h; (*c*) 10% Pd/C, H_2, EtOAc, MeOH, 4.5 bar, 80°C, 15 h; (*d*) DIBAL-H, THF, 0°C to room temp., 2 h; and (*e*) 180°C, 5 min.

to yield anion **9**, which after elimination of nitrite furnishes the cycloheptatriene **10**. The latter then undergoes a sigmatropic [1,5]-hydrogen shift to afford the thermodynamically more stable isomer **6**.

For the synthesis of arcyriacyanin A **1**, an additional nitrogen atom has to be introduced from the beginning. Therefore, we started with methyl (2,6-dinitrophenyl)acetate **11**, which can be prepared from 2,6-dinitrochlorobenzene and

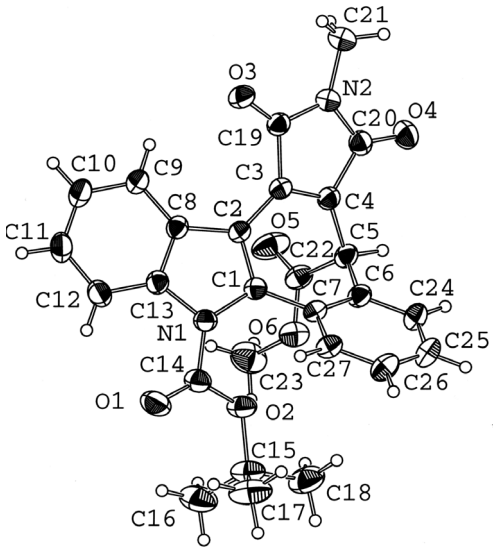


Fig. 1. ORTEP diagram of **6** (numbering differs from that given in the formula).

the anion of dimethyl malonate[10] followed by Krapcho dealkoxycarbonylation.[11] The anion derived from **11** is more stable and less reactive than that obtained from **4**. As a result, in order to achieve cyclization **11** had to be treated with KH at 0°C in the presence of [18]crown-6 and triethylamine. In this way compound **12** was obtained in 40% yield (Scheme 4), and its structure was confirmed by single-crystal X-ray analysis.[7] Reduction of the nitro group by catalytic hydrogenation afforded the amino ester **13**, which subsequently failed to form the oxindole ring either under basic or acidic conditions. However, treatment of amino ester **13** with Otera's 1-hydroxy-3-(isothiocyanato)tetrabutyldistannoxane catalyst[12] furnished the yellow indolin-2-one **14** in 74% yield. Unfortunately, removal of the Boc group[8] under thermal conditions affords an unstable product, and after rapid chromatography, the free indole **15** could only be isolated in 8% yield.

As oxindole **15** was too unstable to undergo further transformations, we decided to prepare the indole directly from the corresponding amino nitrile.[13] The only viable method that we could find to prepare the necessary starting material **17**[14] involved heating cyano ester **16** in DMSO with a hot air gun for a short time (Scheme 5). Immediately after the red colour of the solution had changed to brown, the reaction mixture was poured into ice water to yield a light-brown solid, which was purified by column chromatography on silica gel. In order to avoid polymerization of the product, the solvents had to be removed at 0°C. The yield of nitrile **17** could be increased from 20 to 34% by the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger together with small amounts of 2 N HCl. The deep blue anion of **17** was subsequently allowed to react with bromide **3** to afford the cyclized product **18** in 48% yield. Reduction of the nitro group with dihydrogen in the presence of Pd/C yielded aminonitrile **19**, which upon treatment with diisobutyl aluminium hydride,[15] basic workup, and gel chromatography on Sephadex LH 20 furnished the Boc-protected *N*-methyl-arcyriacyanin A **20** in 12% yield. The low yield obtained for the indole ring closure reflects the unfavourable geometry of the cyano group, which according to the X-ray structural analysis of nitronitrile **18**,[7] adopts a nearly perpendicular relationship with the plane of the seven-membered ring. Furthermore, formation of the planar pyrrole ring causes a higher ring strain than closure of the indolinone ring in **13**. Thermal cleavage of the Boc group[8] in **20** gave *N*-methyl-arcyriacyanin A **21** in 80% yield, and earlier work within our group[1c] has shown that **21** can be converted into **1**.

Although at present the novel condensation technique cannot compete with the Pd-catalyzed syntheses of arcyriacyanin A **1**, it offers an effective route to several *seco* compounds of this series.

Experimental

*Compound **5***

This was obtained as a light yellow, unstable solid, mp 98°C (MeOH). R_F 0.35, EtOAc/hexanes (1 : 3), Merck silica gel 60 F_{254} plates. ν_{max} (KBr)/cm^{-1} 2985, 2955, 1743, 1710, 1639, 1529 (NO_2), 1453, 1385 (NO_2), 1354, 1311, 1259, 1229, 1155, 1073, 746. λ_{max}/nm (log ε) (MeOH) 224 (4.44), 248 (4.26), 302 (sh, 3.81), 393 (3.44). δ_H (400 MHz, $CDCl_3$, TMS) 1.58 (9H, s, Boc), 3.14 (3H, s, NMe), 3.68 (3H, s, OMe), 6.03 (1H, s, H3b), 7.21 (1H, ddd, *J* 8.0, 8.0, 1.0), 7.35 (1H, ddd, *J* 7.3, 7.3, 1.0), 7.41–7.48 (3H, m), 7.56 (1H, s, H8b), 7.57 (1H, ddd, *J* 8.0, 8.0, 1.5), 8.02 (1H, dd, *J* 8.0, 1.5), 8.17 (1H, d, *J* 8.0). δ_C (100 MHz, $CDCl_3$, TMS) 24.3 (NMe), 27.8 (3C, C(CH_3)$_3$), 43.9 (C3b), 53.0 (OMe), 84.7 (*C*(CH_3)$_3$), 108.4, 115.3, 120.5, 123.4, 125.3 (2C), 127.5, 128.2, 128.9, 130.3, 130.7, 133.4, 134.4, 135.5, 136.8, 148.8, 148.9, 168.9, 169.5, 170.5. *m*/*z* (FAB, *m*-NBA) 520 (8%, $[M+1]^{+\bullet}$), 519 (6, $M^{+\bullet}$), 464 (15), 432 (5), 420 (3), 388 (5), 343 (5), 314 (3).

*Compound **6***

This was obtained as a yellow solid, mp 178°C (MeOH) (Found: C 68.6, H 5.2, N 6.0. $C_{27}H_{24}N_2O_6$ requires C 68.6, H 5.1, N 5.9%). R_F 0.46, yellow fluorescence under UV light, EtOAc/hexanes (1 : 3); R_F 0.30 EtOAc/hexanes (1 : 5). ν_{max} (KBr)/cm^{-1} 2984, 2952, 2939 (sh), 1739, 1707, 1640, 1520, 1458, 1435, 1386, 1313, 1289, 1227, 1152, 1120, 1064, 1006, 759. λ_{max}/nm (log ε) (MeOH) 204 (4.63), 247 (4.41), 296 (4.34), 411 (3.33). δ_H (400 MHz, $CDCl_3$, TMS) 1.36 (9H, s, Boc), 3.12 (3H, s, NMe), 3.42 (3H, s, OMe), 5.24 (1H, s, H3b), 7.37–7.53 (6H, m), 8.26 (1H, d, *J* 8.2, H10), 8.36 (1H, d, *J* 7.9, H13). δ_C (100 MHz, $CDCl_3$, TMS) 24.2 (NMe), 27.5 (3C, C(CH_3)$_3$), 45.3 (C3b), 52.6 (OMe), 84.7 (*C*(CH_3)$_3$), 114.0, 114.4 (C10), 123.4 (C13), 123.9, 125.2, 125.5, 126.7, 129.6, 130.1, 130.7, 131.3, 131.8, 132.5, 134.2, 137.8, 141.6, 149.7, 168.5 (C4), 169.4 (C1), 169.5 (C3). *m*/*z* (FAB, *m*-NBA) 473 (11%, $[M+1]^{+\bullet}$), 472 (11, $M^{+\bullet}$), 417 (17), 372 (15), 313 (100). X-Ray crystal analysis: $C_{27}H_{24}N_2O_6$, monoclinic, space group *C*2/*c* (No. 15), *a* 26.328(7), *b* 8.562(2), *c* 21.425(6) Å, β 94.43(2)°, *V* 4815 (2) Å^3, 3341 unique reflections, 2835 with $I > 2\sigma(I)$, R_1 0.0423, wR_2 0.1160 for 322 refined parameters.

*Compound **10***

This was obtained as an oil, R_F 0.51, green fluorescence under UV light, EtOAc/hexanes (1 : 3). δ_H (400 MHz, $CDCl_3$, TMS, −50°C) (*E*)-isomer (3 parts): 1.30 (9H, br s, Boc), 3.19 (3H, s, NMe), 4.13 (3H, s, OMe), 5.24 (1H, br s, H8b), 7.27 (1H, d, *J* 7.9, H5), 7.78 (1H, d, *J* 7.6, H8), 8.25 (1H, d, *J* 7.8, H10), 8.89 (1H, d, *J* 7.9, H13); (*Z*)-isomer (1 part): 1.68 (9H, br s, Boc), 3.19 (3H, s, NMe), 4.06 (3H, s, OMe), 5.36 (1H, br s, H8b), 7.25 (1H, d, *J* 7.9, H5), 7.83 (1H, d, *J* 7.6, H8), 7.85 (1H, d, *J* 7.8, H10), 8.92 (1H, d, *J* 7.9, H13) [overlapping signals: 7.20 (1H, ddd, *J* 7.9, 7.6, 1.0, H12), 7.44 (1H, ddd, *J* 8.7, 7.6, 1.1, H7), 7.60 (1H, ddd, *J* 8.7, 7.9, 1.2, H6), 7.65 (1H, ddd, *J* 7.8, 7.6, 1.2, H11)]. δ_C

(100 MHz, $CDCl_3$, TMS, −50°C, selected) (*E*)-isomer (3 parts): 27.6 ($C(CH_3)_3$), 66.1 (C8b), 82.4 ($C(CH_3)_3$), 115.0 (C10), 125.7 (C8); (*Z*)-isomer (1 part): 28.1 ($C(CH_3)_3$), 65.9 (C8b), 83.8 ($C(CH_3)_3$), 115.5 (C10), 126.0 (C8).

Accessory Material

ORTEP diagrams for compounds **12** and **18**, and experimental data for compounds **7**, **12**–**15**, and **17**–**20** are available from the author or, until July 2009, the *Australian Journal of Chemistry*.

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[7] Crystallographic data (excluding structure factors) for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 190414 (**6**), CCDC 204892 (**12**), and CCDC 214318 (**18**). Copies of the data can be obtained free of charge on application to the CCDC (e-mail: deposit@ccdc.cam.ac.uk).

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