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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6019–6021

A short synthesis of koniamborine, a naturally occurring pyrano[3,2-*b*]indole

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Received 30 May 2007; revised 15 June 2007; accepted 18 June 2007
Available online 23 June 2007

Abstract—An expedient synthesis of the alkaloid koniamborine, the only to date isolated naturally occurring pyrano[3,2-*b*]indole is presented. The key pyrano[3,2-*b*]indole forming step is a palladium-catalyzed reductive N-heteroannulation of 2-(4-methoxy-2-nitrophenyl)-(4*H*)-pyrane-4-one.
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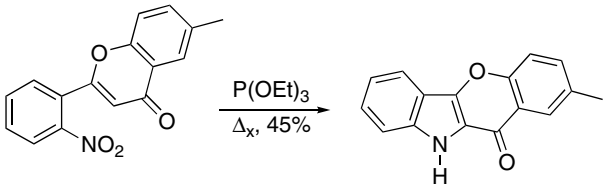
Pyrano[3,2-*b*]indoles are relatively unknown and only around 140 compounds, all but one synthetic, are known. Some of the compounds have a significant antiallergic activity.[1] Pyrano[3,2-*b*]indoles have previously been prepared mainly from condensation of 1-(3-hydroxy-1-methyl-1*H*-indol-2-yl)ethanones with diethyl oxalate in the presence of a base.[1]

A novel alkaloid, koniamborine, was recently isolated from aerial parts of *Boronella koniambiensis* a rutaceous tree endemic to New Caledonia.[2] The structure of koniamborine was elucidated by spectroscopic means including HMBC, HMQC, and NOESY NMR and HRMS and determined to be 7-methoxy-5-methyl-pyrano[3,2-*b*]indol-4(5*H*)-one. The unusual structure of the alkaloid, to our knowledge the only pyrano[3,2-*b*]-indole isolated from natural sources, peaked our interest in its synthesis.

Palladium-catalyzed N-heteroannulation of 2-nitroaryl-substituted alkenes using carbon monoxide as the ultimate reducing agent is emerging as a powerful methodology for the synthesis of a variety of indoles[3] including naturally occurring tjipanazoles,[4] murrayaquinone,[5] bauerine A,[6] carbazole alkaloids,[7] and mushroom metabolites.[8] This methodology has not previously been used for the annulation of 2-(2-nitroaryl)-(4*H*)-pyrane-4-one derivatives. The palladium-catalyzed N-heteroannulation methodology is related to the Cadogan–Sundberg reaction of 2-nitroarylalkenes using ternary phosphites as the reducing agent. A single example of this type of reaction of a 2-nitrophenyl-substituted flavone has been reported (Scheme 1).[9] This result encouraged us to employ the palladium-catalyzed reaction as a key step toward koniamborine.

The synthesis of koniamborine started from commercially available 4-methoxy-2-nitrobenzoic acid. Treatment of this acid with thionyl chloride under standard conditions gave the acid chloride **1** in almost quantitative yield after recrystallization (Scheme 2).[10,11] Formation of the γ-pyrone moiety was achieved under basic conditions using the procedure described in the same year by Korreda and Akagi[12] and Morgan and Ganem.[13] Thus, reaction of freshly prepared **1** with the potassium enolate of 4-methoxy-3-buten-2-one gave the expected γ-pyrone **2** in 77% yield.[14]

Submitting **2** to the annulation conditions previously used to prepare tetrahydrocarbazolones[7] and 3-alkoxyindoles,[3b] bis(dibenzylidenacetone)palladium (6 mol %), 1,3-bis(diphenylphosphino)propane (6 mol %), and



Scheme 1.

Keywords: Annulation; Palladium-catalyzed; Alkaloid.
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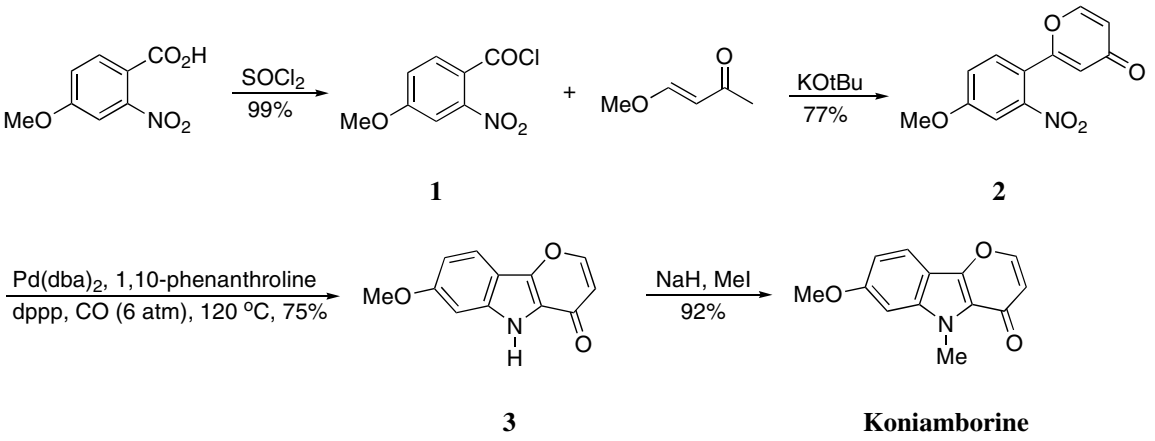
doi:10.1016/j.tetlet.2007.06.092



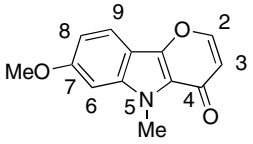
Scheme 2.

1,10-phenanthroline (12 mol %) in the presence of carbon monoxide, gave the expected pyrano[3,2-*b*]indole **3** in good yield.[15] Finally, N-methylation using iodomethane furnished koniamborine in excellent yield.[16]

Analytical data (mp, ^{1}H NMR, and ^{13}C NMR) of the synthetic material confirms the structure of koniamborine as 7-methoxy-5-methyl-pyrano[3,2-*b*]indol-4(5*H*)-one. ^{1}H NMR data for both synthetic and isolated koniamborine are summarized and compared in Table 1. The ^{1}H-resonances were shifted to a lower field by 0.04–0.07 ppm and the ^{13}C-resonances were also at lower field by 0.1–0.4 ppm compared to the isolated compound (see Ref. 16 for a ^{13}C NMR comparison).

In summary, we have synthesized 7-methoxy-5-methyl-pyrano[3,2-*b*]indol-4(5*H*)-one in 52% overall yield in four synthetic steps from commercially available starting material. Analytical data for this compound corroborated the structure of the novel alkaloid koniamborine. We have also shown that 2-(2-nitrophenyl)-(4*H*)-pyrane-4-ones may be used as substrates in palladium-catalyzed reductive N-heteroannulations.

Table 1. ^{1}H NMR data of koniamborine



	δ^a (ppm)	J^a (Hz)	$\Delta\delta$ (ppm)
H-2	7.79 (7.72)	5.9 (6)	0.07
H-3	6.38 (6.32)	5.8 (6)	0.06
H-6	6.76 (6.70)	2.2 (2)	0.06
H-8	6.89 (6.83)	8.9, 2.2 (8, 2)	0.06
H-9	7.76 (7.69)	8.9 (8)	0.07
OMe	3.93 (3.89)		0.04
NMe	4.18 (4.12)		0.06

[a] Literature values in parenthesis.

Acknowledgments

Financial support from the National Science Foundation (CHE-0611096) is gratefully acknowledged. The National Science Foundations Experimental Program to Stimulate Competitive Research (NSF-EPSCoR, 1002165R) is gratefully acknowledged for the funding of a 600 MHz Varian Inova NMR and a Thermo-Finnegan LTQ-FT Mass Spectrometer and the NMR and MS facilities in the C. Eugene Bennett Department of Chemistry at West Virginia University.

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10. *Experimental procedure*: A solution of 4-methoxy-2-nitrobenzoic acid (478 mg, 2.42 mmol) in thionyl chloride (10.6 mL, 145 mmol) was stirred and heated at reflux (6 h) under a positive flow of nitrogen gas. The progress of the reaction was monitored by TLC (hexanes–EtOAc, 1:1). The excess $SOCl_2$ was removed on a rotary evapo-

rator at water aspirator pressure. The resulting tan residue was recrystallized from pentane affording a pale yellow solid (**1**) (520 mg, 2.41 mmol, 99%). Analytical data: mp 54–55 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.95 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.19 (dd, J = 2.5, 8.9 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 164.3 (+), 163.8 (+), 149.4 (+), 133.3 (−), 120.8 (+), 117.1 (−), 110.3 (−), 54.5 (−); IR (neat) 1752, 1605, 1537, 1243 cm^{-1}.

11. Compound **1** has been reported in the literature but we were unable to find any analytical data.
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14. *Experimental procedure*: Potassium 1,1-dimethylethoxide (599 mg, 5.34 mmol) was added to dry THF (12 mL) under a positive flow of nitrogen gas. The flask was cooled to −78 °C and *trans*-methoxy-3-buten-2-one (540 μL, 5.34 mmol) was added drop-wise (10 min). After stirring for 30 min, a solution of freshly prepared acid chloride (**1**) (520 mg, 2.41 mmol) in dry THF (8 mL) was added drop-wise via a cannula over 15 min. The resulting yellow solution was stirred at −78 °C (1 h) then gradually warmed to ambient temperature (3 h). Water (5 mL) was carefully added and the cloudy solution was stirred overnight before diluting with additional water (15 mL). The resulting solution was extracted with diethyl ether (3 × 100 mL), the combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. The crude product was purified by chromatography (hexanes–EtOAc, 1:1 followed by pentane–acetone, 1:1) to afford the product (**2**) (460 mg, 1.86 mmol, 77%) as a pale yellow solid. Analytical data: mp 170–171 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.72 (d, J = 5.9 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.22 (dd, J = 2.6, 8.5 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.39 (dd, J = 2.4, 5.7 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 178.6 (+), 162.6 (+), 161.8 (+), 155.1 (−), 148.7 (+), 132.2 (−), 119.1 (+), 118.9 (−), 117.1 (−), 115.9 (−), 110.6 (−), 56.2 (−); IR (neat) 3052, 1654, 1519, 927 cm^{-1}; HRMS Calcd for $C_{12}H_{10}NO_5$ ($M+H^+$) 248.0559; found, 248.0559. Anal Calcd for $C_{12}H_9NO_5$: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.15; H, 3.38; N, 5.31.
15. *Experimental procedure*: 2-(4-Methoxy-2-nitrophenyl)-4*H*-pyran-4-one (**2**) (140 mg, 0.566 mmol), bis(dibenzylideneacetone)palladium (20.0 mg, 0.0340 mmol), 1,3-bis-(diphenylphosphino)propane (14.0 mg, 0.0340 mmol), and 1,10-phenanthroline monohydrate (13.0 mg, 0.0680 mmol) were dissolved in anhydrous DMF (2 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction vessel was heated at 120 °C under CO (6 atm) for 20 h. Water (10 mL) was added and the brown solution was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed on a rotary evaporator at water aspirator pressure. The resulting crude product was purified by chromatography (pentane–acetone, 8:2 then pentane–acetone, 1:1) to afford **3** (91.0 mg, 0.423 mmol, 75%) as a light tan solid. Analytical data: mp 279–280 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.22 (d, J = 5.7 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 2.2 Hz, 1H), 6.86 (dd, J = 2.0, 8.9 Hz, 1H), 6.39 (d, J = 5.7 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 169.0 (+), 159.9 (+), 153.4 (−), 144.4 (+), 137.5 (+), 123.9 (+), 120.0 (−), 114.0 (−), 112.1 (−), 109.1 (+), 94.4 (−), 55.4 (−); IR (neat) 3143, 1618 cm^{-1}; HRMS Calcd for $C_{12}H_{10}NO_3$ ($M+H^+$) 216.0661; found, 216.0660. Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.69; H, 4.51; N, 6.85.
16. *Experimental procedure*: Sodium hydride (11.0 mg, 0.437 mmol) was washed with hexanes (5 × 1 mL) before adding dry DMF (0.5 mL) under a positive flow of N_2. A solution of 7-methoxypyrano[3,2-*b*]indol-4(5*H*)-one (**3**) (47.0 mg, 0.218 mmol) in DMF (1 mL) was added slowly over 5 min. The resulting orange solution was heated at 60 °C for 30 min followed by slow addition of iodomethane (300 μL, 0.437 mmol). The brown solution was stirred for 1 h at 60 °C before cooling to ambient temperature. DMF was removed via bulb-to-bulb distillation and the crude brown solid was dissolved in diethyl ether (10 mL). The ether solution was washed with brine (3 × 10 mL) and water (3 × 10 mL), the dried ($MgSO_4$), filtered and the solvent was removed on a rotary evaporator at water aspirator pressure. The resulting solid was purified by chromatography (hexanes–ethyl acetate, 6:4) to afford koniamborine (46.0 mg, 0.201 mmol, 92%) as a white solid. Analytical data: mp 141–142 °C (lit. mp 142 °C), ^{13}C NMR (67.5 MHz, $CDCl_3$, lit. values in parenthesis) 171.0 (170.7), 160.6 (160.3), 151.4 (151.3), 145.1 (144.8), 139.0 (138.8), 123.4 (123.1), 120.5 (120.1), 115.3 (115.0), 111.9 (111.6), 109.0 (108.6), 91.7 (91.3), 55.6 (55.3), 31.2 (30.9).