Synthesis of Oxazolylindolyl Alkaloids via Rhodium Carbenoids

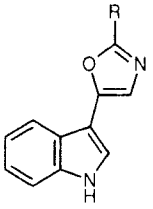
Kevin J. Doyle, Christopher J. Moody*

Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire. LE11 3TU, England

Received 24 May 1994

The oxazolylindole alkaloids pimprinine **(1a)**, pimprinethine **(1b)** and WS-30581 A **(1c)** are readily obtained in two steps by rhodium(II) catalysed reaction of *N*-Boc-3-diazoacetylindole with the appropriate nitrile followed by removal of the Boc-group.

The recently described synthesis of pimprinine type alkaloids from *N*-methyl-3-azidoacetylindole using iminophosphorane chemistry,[1] prompts us to report a complementary approach to the biologically active oxazolylindole alkaloids pimprinine **(1a)**,[2-8] pimprinethine **(1b)**,[4-6,9] and WS-30581A **(1c)**[7] starting from *N*-Boc-3-diazoacetylindole.



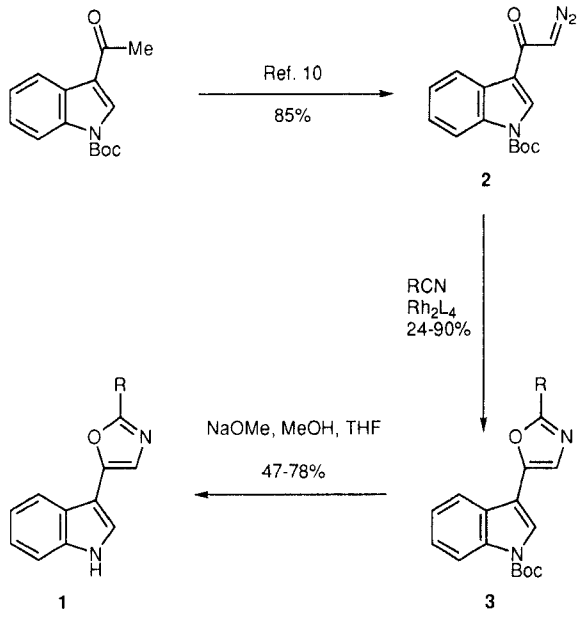
1a	$R = CH_3$	pimprinine
1b	$R = CH_2CH_3$	pimprinethine
1c	$R = CH_2CH_2CH_3$	WS-30581A

The starting diazoketone **2** was readily prepared from *N*-Boc-3-acetylindole using the diazo-transfer procedure described by Danheiser.[10] Slow addition of a chloroform solution of the diazoketone to a mixture of rhodium(II) acetate in acetonitrile at 75 °C gave, after chromatography, the desired oxazolylindole **3a** in 40 % yield, sodium methoxide deprotection of which gave pimprinine **(1a)** (74 %) (Scheme). Interestingly, use of boron trifluoride etherate as catalyst,[11,12] failed to give any of the oxazole **3a**, although use of rhodium(II) trifluoroacetamide[13] at room temperature resulted in a slightly higher yield (46 %).

Reaction of the diazoketone **2** with propionitrile at 75 °C gave the oxazolylindole **3b** (55 %); again rhodium(II) trifluoroacetamide proved to be a more effective catalyst, and repeating the reaction at room temperature resulted in an increase in yield to 90 %. Deprotection of **3b** gave pimprinethine **(1b)** in 78 % yield. Finally, the method was extended to the preparation of the platelet aggregation inhibitor WS-30581 A **(1c)**,[7] by reaction of the diazoketone **2** with butyronitrile (24 % using rhodium(II) trifluoroacetamide as catalyst) followed by deprotection (47 %) as shown in the Scheme.

In summary, the above method constitutes a simple route to the oxazolylindole alkaloids which complements existing methods.

Light petroleum refers to the fraction boiling at 40–60 °C.



Scheme

2-Methyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole (3a):
To a stirred solution of MeCN (5 mL) and rhodium(II) trifluoroacetamide[13] (2.2 mg, 1 % mol equiv) at 25 °C, was added *tert*-butyl 3-diazoacetylindole-1-carboxylate (**2**; 100 mg, 0.35 mmol) dropwise as a solution in EtOH-free $CHCl_3$ (1 mL) over 1 h and the mixture was stirred for a further 2 h. Concentration in vacuo, followed by purification by flash chromatography (eluent: EtOAc/light petroleum) gave the title compound as a pale brown solid; yield: 48 mg (46 %); mp 110–112 °C.

IR (KBr): ν = 1720, 1453, 1371 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.69 (9 H, s), 2.56 (3 H, s), 7.24 (1 H, s), 7.25–7.38 (2 H, m), 7.75 (1 H, d, J = 7.8 Hz), 7.85 (1 H, s), 8.21 (1 H, d, J = 7.9 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.0, 29.2, 84.3, 109.6, 115.5, 120.1, 122.2, 122.3, 123.3, 125.1, 126.7, 135.6, 145.8 (C-5), 149.3, 160.2 (C-2).

MS (EI): *m/z* (%) = 299 (MH^+, 60), 199 (50), 179 (100).

HRMS: *m/z* calc. for $C_{17}H_{18}N_2O_3$ + H 299.1396, found MH^+ 299.1396.

2-Ethyl-5-[3-(*tert*-butoxycarbonyl)indolyl]oxazole (3b):
To a stirred solution of propionitrile (5 mL) and rhodium(II) trifluoroacetamide (2.2 mg, 1 % mol equiv) at 25 °C, was added **2** (100 mg, 0.35 mmol) dropwise as a solution in EtOH-free $CHCl_3$ (1 mL) over 1 h and the mixture was stirred for a further 2 h. Concentration in vacuo, followed by purification by flash chromatography (eluent: EtOAc/light petroleum) gave the title compound as a pale brown glassy solid; yield: 100 mg (90 %).

IR ($CDCl_3$): ν = 1744, 1451, 1370 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.42 (3 H, t, J = 7.5 Hz), 1.70 (9 H, s), 2.90 (2 H, q, J = 7.6 Hz), 7.31–7.43 (3 H, m), 7.80 (1 H, d, J = 7.1 Hz), 7.86 (1 H, s), 8.21 (1 H, d, J = 7.8 Hz).

MS (EI): *m/z* (%) = 312 (M^+, 20), 256 (30), 212 (40), 57 (100).

HRMS: *m/z* calc. for $C_{18}H_{20}N_2O_3$ 312.1474, found 312.1474.

2-Propyl-5-[3-(1-*tert*-butoxycarbonyl)indolyl]oxazole (3c):
To a stirred solution of butyronitrile (5 mL) and rhodium(II) trifluoroacetamide (12 mg, 1% mol equiv) in EtOH-free $CHCl_3$ (5 mL) at 25 °C, was added **2** (570 mg, 2 mmol) dropwise as a solution in EtOH-free $CHCl_3$ (20 mL) over a 2 h period. After stirring for 12 h the mixture was concentrated in vacuo. Purification by flash chromatography (eluent: CH_2Cl_2/Et_2O) gave the title compound as a pale brown glassy solid; yield: 153 mg (24%).

IR ($CDCl_3$): ν = 1743, 1451, 1371 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.05 (3 H, t, J = 7.4 Hz), 1.71 (9 H, s), 1.80–1.95 (2 H, m), 2.82 (2 H, t, J = 7.4 Hz), 7.31–7.39 (2 H, m), 7.74–7.78 (1 H, m), 7.84 (1 H, s), 8.21–8.28 (2 H, m).

MS (EI): m/z (%) = 326 (M^+, 10), 270 (40), 226 (40), 57 (100).

HRMS: m/z calc. for $C_{19}H_{22}N_2O_3$ 326.1630, found 326.1630.

Pimprinine [2-methyl-5-(3-indolyl)oxazole] (1a):
To a stirred solution of **3a** (86 mg, 0.29 mmol) in THF (5 mL) under an N_2 atmosphere was added NaOMe (30% solution in MeOH 1.5 mL, 3 equiv) dropwise. After 15 min the mixture was diluted with Et_2O (3 mL) and washed with H_2O (2 × 3 mL), brine (3 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (eluent: EtOAc) gave the title compound; yield: 42 mg (74%); mp 202–203 °C (Lit.[6] mp 204–205 °C).

IR (KBr): ν = 3426, 1638, 1453, 1023 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.53 (3 H, s), 7.14 (1 H, s), 7.21–7.29 (2 H, m), 7.42 (1 H, d, J = 7.5 Hz), 7.50 (1 H, d, J = 2.6 Hz), 7.82 (1 H, d, J = 7.7 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 106.0, 111.4, 119.9, 120.0, 120.8, 121.3, 123.0, 124.0, 136.1, 147.2 (C-5), 159.1 (C-2).

HRMS: m/z calc. for $C_{12}H_{10}N_2O$ + H 199.0871, found MH^+ 199.0871.

Pimprinethine [2-ethyl-5-(3-indolyl)oxazole] (1b):
To stirred solution of **3b** (100 mg, 0.32 mmol) in THF (5 mL) under an N_2 atmosphere was added NaOMe (30% solution in MeOH, 1.5 mL, 3 equiv) dropwise. After 15 min the mixture was diluted with Et_2O (3 mL) and washed with H_2O (2 × 3 mL), brine (3 mL), dried ($MgSO_4$) and then concentrated in vacuo. Purification by flash chromatography (eluent: EtOAc) gave the title compound; yield: 53 mg (78%); mp 152–154 °C (Lit.[9] mp 161 °C).

IR (KBr): ν = 3174, 1635, 1444, 1351, 1117 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (3 H, t, J = 7.6 Hz), 2.87 (2 H, q, J = 7.6 Hz), 7.14 (1 H, s), 7.25 (2 H, m), 7.42 (1 H, m), 7.50 (1 H, d, J = 2.6 Hz), 7.83 (1 H, d, J = 7.7 Hz), 8.36 (1 H, br s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 21.6, 106.1, 111.4, 119.8, 119.9, 120.7, 121.3, 123.0, 124.0, 136.1, 147.0 (C-5), 163.6 (C-2).

MS (EI): m/z (%) = 212 (M^+, 100), 197 (30), 142 (40).

HRMS: m/z calc. for $C_{13}H_{12}N_2O$ 212.0950, found 212.0950.

WS-30581 A [2-propyl-5-(3-indolyl)oxazole] (1c):
To a stirred solution of **3c** (153 mg, 0.48 mmol) in THF (5 mL) under an N_2 atmosphere was added NaOMe (30% solution in MeOH, 2.0 mL, 3 equiv) dropwise. After 15 min the mixture was diluted with Et_2O (3 mL) and washed with H_2O (2 × 3 mL), brine (3 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (eluent: EtOAc/light petroleum) gave the title compound, yield: 52 mg (47%); mp 131–133 °C (Lit.[7] mp 128–130 °C).

IR (KBr): ν = 3150, 1637, 1617, 1459, 1252 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.06 (3 H, t, J = 7.3 Hz), 1.87 (2 H, m), 2.84 (2 H, t, J = 7.3 Hz), 7.18 (1 H, s), 7.21–7.31 (2 H, m), 7.43 (1 H, dd, J = 1.9, 6.2 Hz), 7.52 (1 H, d, J = 2.6 Hz), 7.85 (1 H, dd, J = 2.7, 6.8 Hz), 8.93 (1 H, br s).

^{13}C NMR (62.5 MHz, $CDCl_3$): 13.7, 20.6, 30.1, 105.8, 111.5, 119.6, 119.9, 120.7, 121.6, 122.8, 124.1, 136.2, 147.2 (C-5), 162.7 (C-2).

MS (EI): m/z (%) = 226 (M^+, 100), 197 (50), 142 (80).

HRMS: m/z calc. for $C_{14}H_{14}N_2O$ 226.1106, found 226.1106.

We thank Fisons Pharmaceuticals for their generous support of our research, Professor Pedro Molina for helpful discussions (made possible by a grant under the Acciones Integradas Scheme), and Drs J.A. Ballantine and O.W. Howarth at the SERC MS and NMR Services respectively.

(1) Molina, P.; Fresneda, P.M.; Almendros, P. *Synthesis* **1993**, 54.
(2) Bhate, D.S.; Hulyalker, R.K.; Menon, S.K. *Experientia* **1960**, *16*, 504.
(3) Joshi, B.S.; Taylor, W.I.; Bhate, D.S.; Karmarkar, S.S. *Tetrahedron* **1963**, *19*, 1437.
(4) Yoshioka, T.; Mohri, K.; Oikawa, Y.; Yonemitsu, O. *J. Chem. Res. (S)* **1981**, 194.
(5) Koyama, Y.; Yokose, K.; Dolby, L. *J. Agric. Biol. Chem.* **1981**, *45*, 1285.
(6) Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457.
(7) Umehara, K.; Yoshida, K.; Okamoto, M.; Iwami, M.; Tanaka, H.; Kohsaka, M.; Imanaka, H. *J. Antibiot.* **1984**, *37*, 1153.
(8) Somei, M.; Sato, H.; Komura, N.; Kaneko, C. *Heterocycles* **1985**, *23*, 1101.
(9) Noltenmeyer, M.; Sheldrick, G.M.; Hoppe, H.-U.; Zeeck, A. *J. Antibiot.* **1982**, *35*, 549.
(10) Danheiser, R.L.; Müller, R.F.; Brisbois, R.G.; Park, S.Z. *J. Org. Chem.* **1990**, *55*, 1959.
(11) Doyle, M.P.; Buhro, W.E.; Davidson, J.G.; Elliott, R.C.; Hoekstra, J.W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657.
(12) Ibata, T.; Isogami, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 618.
(13) Cox, G.G.; Kulagowski, J.J.; Moody, C.J.; Sie, E.-R.H.B. *Synlett* **1992**, 975.