Synthesis of Novel Oxazolyl-indoles

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Received 10 July 2006

Abstract: We describe the synthesis of oxazolyl-indoles that are structurally related to pimprinaphine. The effect of the indole N-cyanoalkyl substituents on the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxidation was evaluated.

Key words: oxazolyl-indoles, Yonemitsu reaction, DDQ-mediated oxidation, cyclizations, coupling

Pimprinaphine (1) is a 2,5-disubstituted (3-indolyl)oxazole that was isolated from Streptoverticillum olivoreticuli (Figure 1).1,2 The related (3-indolyl)oxazole pimprinine (2) was isolated from Streptomyces pimprina, pimprinethine (3) was isolated from Streptomyces cinna- moneus, and WS-30581A (4) and WS-30581B (5) were isolated from Streptoverticillum waksmanii.3,4 All of these compounds 1–5 show interesting biological activities. For example, pimprinine (2) inhibits monoamine oxidase (MAO) and has an anti-epileptic effect, while compounds 4 and 5 have potent inhibitory effects on platelet aggregation. Recently, Pettit and co-workers isolated the new oxazolyl-indoles in this series, labradorin 1 (6) and labradorin 2 (7), from Pseudomonas syringae, which were found to be potent inhibitors against human cancer cells.5 Oxazole subunits are also found in other biologically active natural products.5 Although the syntheses of 1–7 have been reported,7 bis(indolyl)oxazoles related to pimprinaphine (1) are unknown in the literature.

We herein describe the synthesis of novel bis(indolyl)oxazoles 8, 9 and the parent compound 10.

For the synthesis of 8 and 9, tryptamine hydrochloride was first protected using di-tert-butyl dicarbonate in the presence of triethylamine to furnish 11 in quantitative yield.9 Cyanoalkyl groups were then attached to the indole nitrogen of 11 to furnish 12 and 13 in 67% and 60% yields, respectively (Scheme 1).

Scheme 1

Figure 1
Compounds 12 and 13 were then subjected to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated oxidation to give the desired products 14 and 15, respectively (Scheme 2). A small difference in yields was observed in this DDQ-mediated oxidation.

To study the DDQ-mediated oxidation more carefully, we subjected compound 16, prepared from 11, to the same reaction conditions (Scheme 3). A striking reduction in yield and rate of reaction was observed in the preparation of 17. The DDQ-mediated oxidation was found to be very difficult for 16, which we believe could be due to the electron-withdrawing effect of the cyanomethyl substituent. A longer reaction time was required even in the presence of three equivalents of DDQ. We have previously observed a similar effect in the Pd(II)-catalyzed oxidative cyclization of a bisindolylmaleimide bearing a cyanomethyl functionality.8a

Scheme 2

The Boc groups of 14 and 15 were deprotected using trifluoroacetic acid to furnish the free amine as a trifluoroacetic acid salt in quantitative yield (Scheme 4).10 The crude products 18 and 19, which were reasonably pure by proton-NMR, were used in the next step without further purification. Coupling of 18 and 19 with N-methylindoled-3-acetic acid (20)11 in the presence of N-ethyl-N’-(3-dimethylaminopropyl)carbodiimide and N-hydroxybenzotriazole gave the ketoamides 21 and 22 in 70% and 63% yields, respectively. Finally, compounds 21 and 22 were treated with triphenylphosphine and iodine in the presence of triethylamine12 to furnish the target oxazoles 8 and 9. A higher yield was obtained for oxazole 9 whereas a lower yield was registered for 8, perhaps due to the decomposition of the starting material 21 via a retro-Michael reaction and loss of acrylonitrile in the presence of triethylamine.

In an initial biological study, an in vitro proliferation assay of the new oxazolyl-indole 9 was performed. A dose-dependent proliferative response of murine T cells was apparent when cells were stimulated with oxazole 9 at a concentration range of 2–8 nM.13,14 Further biological evaluation of these compounds is in progress.
In order to synthesize 10, we acylated indole with chloroacetyl chloride in pyridine to furnish 23 (Scheme 5). The azide treatment with sodium azide in acetone–water in 97% yield. The azide 24 was easily converted to the amine hydrochloride 25 in excellent yield by hydrogenation over palladium-on-carbon in the presence of hydrochloric acid hydrochloride. 17 No column chromatography was necessary for the preparation of the hydrochloride salt 25 from indole via this three-step sequence.

The amine hydrochloride 25 could be coupled with indole-3-acytic acid (26) in the previous manner to produce the corresponding ketoamide, but we decided on a different method. In the event, coupling of the azide 24 with indole-3-acytic acid (26) in the presence of trimethylphosphine in tetrahydrofuran–toluene furnished ketoamide 27 in high yield (Scheme 6). N-unsubstituted ketoamide 27 did not furnish the oxazole 10 upon treatment with triphenylphosphine and iodine even in the presence of excess triethylamine. Ketoamide 27 was finally treated with phosphorus oxychloride in pyridine to furnish the target molecule 10 in good yield.

In summary, we have synthesized novel bis(indolyl)oxazoles 8, 9 and 10. A strong deactivating effect was observed for the DDQ-mediated oxidation of indole 16 bearing an N-cyanomethyl group, indicating that an electron-withdrawing group in simple indoles would generally disfavor the Yonemitsu oxidation.

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. 1H and 13C 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 CH2Cl2 were prepared by a solvent purification system. All other solvents (analytical grade) including anhydrous solvents and reagents were used as received. All experiments were performed under a nitrogen atmosphere.

1,1-Dimethyl[2-(1H-indol-3-yl)ethyl]carbamate (11)
To a stirred solution of tryptamine hydrochloride (5.90 g, 30 mmol) and Et3N (12.7 mL, 90 mmol) in dioxane (25 mL) at r.t. was added dropwise a solution of Boc2O (7.20 g, 33 mmol) in dioxane (25 mL). The mixture was stirred at r.t. for 24 h. EtOAc (150 mL) was added and the mixture was washed with H2O (3 × 100 mL), brine (100 mL) and then dried over Na2SO4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 2:1) to yield the desired product (7.81 g, 100%) as a white solid.

Mp 88–90 °C (Lit.9 94–95 °C).

IR (thin film): 3411, 3327, 2976, 1692, 1512, 1457, 1366, 1250, 119.7, 119.5, 117.5, 113.4, 108.8, 67.0, 58.9, 41.9, 28.4, 25.8, 19.1.

1H NMR (500 MHz, CDCl3): δ = 8.27 (br s, 1 H), 7.62 (d, J = 7.9 Hz, 1 H), 7.38 (d, J = 7.9 Hz, 1 H), 7.21–7.24 (m, 1 H), 7.13–7.16 (m, 1 H), 7.02 (s, 1 H), 4.67 (br s, 1 H), 3.48 (m, 2 H), 2.97 (t, J = 6.7 Hz, 2 H), 1.47 (s, 9 H).

13C NMR (125 MHz, CDCl3): δ = 156.3, 136.6, 127.5, 122.3, 119.5, 118.9, 113.1, 111.4, 79.4, 41.1, 28.6, 26.0.

1,1-Dimethyl[2-[1-(2-cyanoethyl)-1H-indol-3-yl]ethyl]carbamate (12)
To a stirred solution of 11 (2.60 g, 10 mmol) and acrylonitrile (1.4 mL, 20 mmol) in dioxane–THF (60 mL, 1:1) at 0 °C was added dropwise a catalytic amount (0.5 mL) of Triton-B (40% benzyltrimethylammonium hydroxide solution in MeOH). The reaction mixture was stirred for 4 h allowing it to warm to r.t. It was then heated at 70 °C for 2 h. The mixture was cooled to r.t. and poured into H2O (50 mL). It was acidified with HCl (0.5 N, 25 mL) and the aq phase was extracted with EtOAc (2 × 75 mL). The combined organic layer was washed with H2O (50 mL), brine (50 mL) and dried over MgSO4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 1:1) to yield the desired product (2.09 g, 67%) as a white solid.

Mp 85–87 °C.

IR (thin film): 3415, 2975, 2932, 2251, 1700, 1512, 1467, 1366, 1250, 1172, 743 cm–1.

1H NMR (500 MHz, CDCl3): δ = 7.62 (d, J = 7.9 Hz, 1 H), 7.24–7.30 (m, 2 H), 7.14–7.17 (m, 1 H), 6.98 (s, 1 H), 4.36 (t, J = 6.7 Hz, 2 H), 3.43 (m, 2 H), 2.93 (t, J = 6.7 Hz, 2 H), 2.75 (t, J = 6.7 Hz, 2 H), 1.45 (s, 9 H).

13C NMR (125 MHz, CDCl3): δ = 156.0, 135.8, 128.4, 125.3, 122.3, 119.7, 119.5, 117.5, 113.4, 108.8, 67.0, 58.9, 41.9, 28.4, 25.8, 19.1.
3.15 (d, $J = 5.8$ Hz, 2 H), 4.58 (t, $J = 6.1$ Hz, 1 H), 7.71 (d, $J = 8.2$ Hz, 1 H), 8.17 (d, $J = 7.6$ Hz, 1 H), 1.46 (s, 9 H), 4.28 (t, $J = 6.4$ Hz, 2 H), 3.46 (m, 2 H), 2.96 (t, $J = 7.0$ Hz, 2 H), 2.25–2.28 (m, 2 H), 2.19 (quin, $J = 6.7$ Hz, 2 H), 1.46 (s, 9 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 156.1, 136.4, 128.3, 125.7, 122.3, 119.5, 118.9, 112.9, 109.3, 44.3, 43.2, 28.6, 26.2, 25.9, 14.8.$

MS (EI): $m/z (%) = 327$ [M$^+$], 271, 254, 210, 197 (100), 143, 130. HRMS (EI): $m/z$ calc for C$_{18}$H$_{21}$N$_3$O$_3$: 327.1580; found: 327.1587.

1,1-Dimethyl[2-(1-cyanomethyl-1H-indol-3-yl)ethyl]carbamate (16)

To a stirred suspension of NaH (60% dispersion in mineral oil, 0.84 g, 21 mmol) in DMF (10 mL) at 0 °C was added dropwise a solution of 11 (3.65 g, 14 mmol) dissolved in DMF (15 mL). The mixture was stirred at 0 °C for 30 min and then a solution of bromoacetonitrile (2.11 g, 17.5 mmol) in DMF (10 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 24 h. Then another portion of bromoacetonitrile (0.42 g) was added and the reaction was stirred for a further 12 h. It was then cooled to 0 °C and diluted with Et$_2$O (10 mL). H$_2$O (100 mL) was added very slowly. The aq phase was extracted with Et$_2$O (2 × 50 mL) and then EtOAc (2 × 50 mL). The combined organic phases were washed with H$_2$O (3 × 100 mL), brine (100 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 1:2) to yield the desired product (2.55 g, 61%) as a white solid.

Mp 99–101 °C.

IR (thin film): 3417, 3354, 2976, 2931, 1694, 1614, 1513, 1465, 1366, 1250, 1171, 743 cm$^{-1}$.

$^{1}$H NMR (500 MHz, CDCl$_3$): $\delta = 7.64$ (d, $J = 7.9$ Hz, 1 H), 7.34 (d, $J = 8.2$ Hz, 1 H), 7.25–7.28 (m, 1 H), 6.96 (s, 1 H), 4.68 (br, 1 H), 4.28 (t, $J = 6.4$ Hz, 2 H), 3.46 (m, 2 H), 2.96 (t, $J = 7.0$ Hz, 2 H), 2.25–2.28 (m, 2 H), 2.19 (quin, $J = 6.7$ Hz, 2 H), 1.46 (s, 9 H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 156.1, 136.4, 128.3, 125.7, 122.3, 119.5, 118.9, 112.9, 109.3, 44.3, 43.2, 28.6, 26.2, 25.9, 14.8.$

MS (EI): $m/z (%) = 327$ [M$^+$]. Synthesis 2006, No. 23, 3948–3954 © Thieme Stuttgart · New York
N-[(2-(Cyanoethyl)-1H-indol-3-yl)-2-oxoethyl]-1-methyl-1H-indole-3-acetamide (21)

To a mixture of amine trifluoroacetate 19 (0.87 g, 2.45 mmol), 1-methylindole-3-acetic acid (1.40 g, 7.35 mmol), EDCl-H2O (1.41 g, 7.35 mmol), HOBT·H2O (0.99 g, 7.35 mmol) and NaHCO3 (3.09 g, 36.75 mmol) at r.t. was added DMF (25 mL). The mixture was stirred at r.t. for 24 h. It was then poured into sat. aq NaHCO3 solution (100 mL) and extracted with EtOAc (2 × 100 mL). The organic phase was washed with HCl (1 N, 100 mL), H2O (100 mL), brine (100 mL) and dried over MgSO4. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH2Cl2-MeOH, 95:5) to yield the desired product (0.64 g, 63%) as a yellowish-white solid.

IR (thin film): 3392, 3053, 2935, 2247, 1646, 1527, 1467, 1394, 1215, 1161, 1073, 919, 744 cm⁻¹.

HRMS (EI): m/z (%) = 412 [M⁺], 394, 285, 228, 211 (100), 197, 171, 144, 129, 77.

HRMS (EI): m/z calculated for C25H23N4O4: 412.1899; found: 412.1892.

HRMS (EI): m/z calculated for C24H20N4O: 380.1641; found: 380.1637.

HRMS (EI): m/z calculated for C23H22N2O: 380.1641; found: 380.1637.
chromatography on silica gel (CH₂Cl₂–hexanes, 95:5) to yield the desired product (56 mg, 71% yield) as a yellow oil.

IR (thin film): 1693, 1635, 1613, 1467, 1373, 1172, 742 cm⁻¹.

1H NMR (500 MHz, DMSO-d₆): δ = 7.82 (d, J = 7.9 Hz, 1 H), 7.76 (s, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 1 H), 7.40 (d, J = 8.2 Hz, 1 H), 7.34 (s, 1 H), 7.25 (t, J = 7.0 Hz, 1 H), 7.14–7.17 (m, 2 H), 1.05 (t, J = 7.0 Hz, 1 H), 4.28 (t, J = 7.3 Hz, 4 H), 3.76 (s, 3 H), 2.46 (t, J = 7.0 Hz, 2 H), 2.09 (quin, J = 7.0 Hz, 2 H).

13C NMR (125 MHz, DMSO-d₆): δ = 158, 144, 84.


2-Chloro-1-(1H-indol-3-yl)ethanone Hydrochloride (25)

To a stirred solution of 24 (200 mg, 1 mmol) in MeOH (10 mL) was carefully added Pd/C (50 mg) followed by HCl (0.5 mL). The flask was fitted with a three-way stop-cock connected to a H₂-filled balloon and the air inside the flask was removed. The reaction mixture was stirred with H₂ for 24 h. The solid precipitate was filtered through a sintered glass funnel to yield the desired product (1.24 g, 75%) as a yellowish solid.

Mp 220–222 °C (dec).

1H NMR (500 MHz, DMSO-d₆): δ = 12.03 (br s, 1 H), 10.92 (s, 1 H), 8.42 (s, 1 H), 8.16–8.18 (d, 2 H), 7.61 (d, J = 7.9 Hz, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 1 H), 7.29 (s, 1 H), 7.18–7.24 (m, 2 H), 7.08 (t, J = 7.5 Hz, 1 H), 6.99 (t, J = 7.3 Hz, 1 H), 4.50 (d, J = 4.9 Hz, 2 H), 3.66 (s, 2 H).

13C NMR (125 MHz, DMSO-d₆): δ = 190.3, 171.1, 136.4, 136.1, 133.7, 127.3, 125.4, 124.0, 122.9, 121.9, 121.2, 121.0, 118.8, 118.4, 114.0, 112.2, 111.3, 108.8, 45.9, 32.6.

ESI-MS: m/z = 332 [M + H]+.


3-[(3-Indolyl)methyl]-5-oxazolyl-1H-indole (10)

To a stirred solution of 27 (33 mg, 0.1 mmol) in pyridine (2.5 mL) at rt was added dropwise POCl₃ (0.5 mL, 5.5 mmol). The mixture was stirred at rt for 3 h. It was then diluted with EtOAc (25 mL) and poured into an ice-cold sat. NaHCO₃ solution (50 mL). The organic phase was washed with aq 5% NaOH solution (20 mL). The aq phase was extracted with EtOAc (3 × 50 mL) and the combined organic extract was then washed with H₂O (50 mL) and brine (50 mL) and dried over Na₂SO₄. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH₂Cl₂–MeOH, 9:1) to yield the desired product (26 mg, 83%) as a light yellow solid.

Mp 200–202 °C (dec).

1H NMR (500 MHz, acetone-d₆): δ = 10.64 (br s, 1 H), 10.18 (br s, 1 H), 7.83–7.85 (m, 1 H), 7.73–7.74 (m, 1 H), 7.66 (s, 1 H), 7.47 (d, J = 7.9 Hz, 1 H), 7.39–7.41 (m, 1 H), 7.36 (s, 1 H), 7.24–7.25 (m, 1 H), 7.18–7.21 (m, 1 H), 7.10–7.15 (m, 2 H), 7.04–0.07 (m, 1 H), 4.32 (s, 2 H).

13C NMR (125 MHz, acetone-d₆): δ = 162.0, 148.9, 137.7, 128.4, 125.1, 124.3, 123.4, 123.2, 122.4, 121.1, 120.6, 120.4, 119.7, 112.7, 112.2, 110.6, 106.0, 25.5.

ESI-MS: m/z = 314 [M + H]+.


Acknowledgment

This investigation was supported in part by the donors of the Petroleum Research Fund (PRF), administered by the American Chemical Society, and Wyeth.