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First Synthesis of 5-Chloro-7-[1,3]oxazolo[4,5-b]pyridin-2-ylquinolin-8-ol by Pd-Catalyzed Arylation

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Abstract: 5-Chloro-7-[1,3]oxazolo[4,5-b]pyridin-2-ylquinolin-8-ol was synthesized by a Pd-catalyzed arylation, which proceeds efficiently with 2 equivalents of benzylated clioquinol and 1 equivalent of oxazolo[4,5-b]pyridine. The product was smoothly debenzylated by boron trichloride in dichloromethane.

Keywords: Arylation, clioquinol, oxazolopyridine, palladium, synthesis

In the search for biologically active compounds as potential drug candidates, the efficient synthesis of both libraries and individual heterocyclic small molecules is of major importance to the pharmaceutical industry. Benzoxazoles[1] and their derivatives[2] are key components of natural products, pharmaceuticals, and their synthetic intermediates.[3] For example, they find application in drug discovery as melatonin receptor agonists,[4] cyclooxygenase (COX) inhibitors,[5] anticancer agents,[6] and 5-HT3 receptor antagonists.[7]

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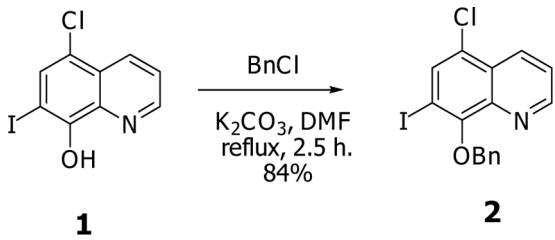
Interestingly, the oxazolopyridine moiety is far less common in the literature, although it might offer some advantages from a medicinal chemistry point of view. The pyridine fragment may provide better water solubility by offering an additional site for protonation or it might enhance intermolecular interactions with a target protein by formation of an additional hydrogen bond.

Clioquinol **1**, a derivative of 8-hydroxyquinoline, is a monoprotic bidentate metal chelator of copper, zinc, and iron. It was first prepared in Germany in the early part of the past century and has been widely used for many years as an antimicrobial agent for the treatment of diarrhea and skin infections. More recently, because it binds copper and zinc, metals essential for the activity of the enzyme superoxide dismutase-1 (SOD1), it has been featured as a potential treatment for Alzheimer's disease.[8] In the 1970s, it was linked to an outbeak of subacute myelo-optic neuropathy in Japan and was banned in many countries.[9]

Approaches involving arylation of oxazolo[4,5-b]pyridine **3** by palladium (pd)–catalyzed coupling have been successfully developed[10] and used to explore the arylation of oxazolo[4,5-b]pyridine **3** with benzylated clioquinol **2**.

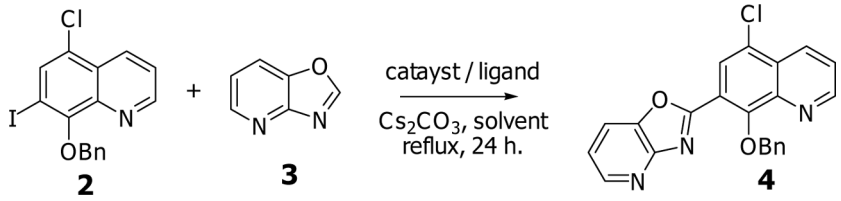
Clioquinol **1** was smoothly benzylated in dimethylformamide (DMF) with benzyl chloride (BnCl) in the presence of K_2CO_3 to provide a good yield of O-benzyl clioquinol **2** (Scheme 1).[11] Oxazolo[4,5-b]pyridine **3** was prepared by the known procedure.[12] Initial attempts to effect the Pd-catalyzed arylation of **3** with **2** under conditions for literature-related processes were unsuccessful (Table 1, entries 1–6). Variation of the Pd source was then examined. The compounds $Pd_2(dba)_3/PPh_3$ in refluxing acetone worked but gave a poor yield of arylation product **4** (Table 1, entry 7). Further optimization, using CH_3CN as the solvent, afforded **4** in 35% yield while changing the ligand to tri-2-furylphosphine (TFP) decreased the yield to 30% (Table 1, entry 8). The effect of ligand indicated that steric factors appeared to be some of the essential control elements. Tri-2-furylphosphine was found to be as efficient as



1 **2**

Scheme 1. Benzylation of clioquinol **1**.

Table 1. Arylation of oxazolo[4,5-b]pyridine (**3**) with 8-(benzyloxy)-5-chloro-7-iodoquinoline (**2**) by Pd catalyst[a]



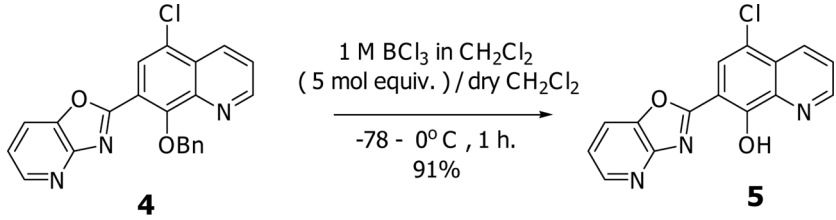
Entry	Solvent	Catalyst/ligand	Yield (%)[b]
1	Acetone	$Pd(OAc)_2/PPh_3$	—[c]
2	Acetone	$Pd(OAc)_2/PPh_3$	—
3	Acetone	$Pd(PPh_3)_4$	—
4	CH_3CN	$Pd(OAc)_2/PPh_3$	—
5	DMF	$Pd(OAc)_2/PPh_3$	—
6	Acetone	$Pd_2(dba)_3/PPh_3$	5
7	CH_3CN	$Pd_2(dba)_3/PPh_3$	35
8	CH_3CN	$Pd_2(dba)_3$/TFP	30
9	CH_3CN	$Pd_2(dba)_3/PPh_3$	70[d]
10	CH_3CN	$Pd_2(dba)_3/PPh_3$	40[e]

[a]Conditions: **2** (2 mol equiv), **3** (1 mol equiv), 5 mol% Pd, 20 mol% ligand, and Cs_2CO_3 (2 mol equiv).
[b]Isolated yield.
[c]Reaction run at room temperature; no product was detected.
[d]10 mol% Pd, 40 mol% PPh_3.
[e]10 mol% Pd, 20 mol% PPh_3.

the marginally larger PPh_3. An excess of O-benzyl clioquinol **2** together with increased amount of catalyst (10 mol%) and ligand (40 mol%) gave a 75% yield of **4** (Table 1, entry 9). A 4:1 molar ratio of $Pd_2(dba)_3/PPh_3$ was important for maintaining catalytic efficiency, because lowering the amount of triphenyl phosphine from 40 to 20 mol% decreased the yield (Table 1, entry 10).

The O-benzyl group of **4** was easily cleaved with boron trichloride in dichloromethane (DCM) at −78 to 0°C (BCl_3/CH_2Cl_2) to provide 5-chloro-7-[1,3]oxazolo[4,5-b]pyridin-2-ylquinolin-8-ol **5** (Scheme 2).

In conclusion, the first synthesis of 5-chloro-7-[1,3]oxazolo[4,5-b] pyridin-2-ylquinolin-8-ol **5** by Pd-catalyzed arylation is reported. The arylation proceeds efficiently with 2 equivalents of *o*-benzyl clioquinol **2** and 1 equivalent of oxazolo[4,5-b]pyridine **3** using $Pd_2(dba)_3$ and PPh_3 as catalyst and ligand, respectively, to provide the arylated product, which was readily debenzylated by BCl_3 at −78 to 0°C.



Scheme 2. Debenzylation of compound **4**.

EXPERIMENTAL

All reagents were commercially available and used without purification. Flash-column chromatography was performed using silica gel 60 (230–400 mesh). Melting points were determined on a Kofler hot-stage apparatus. Microanalyses were obtained using a Carlo Erba Elemental Analyzer model 1106. Accurate molecular masses were recorded on a micro-TOF machine. Infrared (IR) spectra were recorded using a Perkin-Elmer Fourier transform (FT)–IR spectrometer. Nuclear magnetic resonance (NMR) spectra were determined at 500 MHz (^{1}H) and at 75 Mz (^{13}C) on Bruker spectrometers. Chemical shift values are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS), and coupling constants are in hertz. Chemical shift multiplicities are reported as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad; br s, broad singlet; app. t, apparent triplet. Oxazolo[4,5-b]pyridine **3** was prepared according to the literature method.[12]

8-(Benzyloxy)-5-chloro-7-iodoquinoline (2)

Clioquinol **1** (5.0 g, 16.37 mmol) was dissolved in DMF (17 mL) and K_2CO_3(4.52 g, 32.74 mmol), and benzyl chloride (2.28 g, 18.0 mmol) added. The resulting mixture was stirred and heated under reflux for 2.5 h, cooled, poured into water, and extracted with CH_2Cl_2 (2×20 mL). The organic layer was separated and washed with water (3×50 mL), dried (Na_2SO_4), and evaporated. Crystallization of the residue from ethyl acetate yielded the product (5.50 g, 13.91 mmol, 85%), which crystallized as yellow needles from ethyl acetate, mp 105–106°C. IR (solid): 3063, 3033, 2967, 2941, 2884, 1949, 1810, 1733, 1598, 1572, 1482, 1448, 1390, 1350, 1273, 1207, 1133, 1081, 1037, 960, 941, 908, 867, 843, 810, 790, 760, 723, 695, 665, 614, 603, 556, 483 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.0$ (1H, dd, $J = 4.27$ and 1.71, ArH), 8.5 (1H, dd, $J = 8.55$ and

1.71, ArH), 7.9 (1H, s, ArH), 7.6 (2H, d, $J = 7.3$, $2 \times$ ArH), 7.5 (1H, dd, $J = 8.55$ and 4.27, ArH), 7.4 (1H, t, $J = 7.3$, ArH), 7.2–7.3 (2H, m, ArH), 5.4 (2H, s, CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.8$, 137.4, 135.5, 133.9, 129.2, 128.8, 128.6, 127.9, 127.0, 122.7, 91.2, 76.9. MS (ES^+): m/z (%) = 396 (^{35}Cl MH^+, 100), 398 (^{37}Cl MH^+, 30). Anal. calcd. for $C_{16}H_{11}ICINO$: C, 48.57; H, 2.80; Cl, 8.96; I, 32.08; N, 3.54. Found: C, 48.50; H, 2.75; Cl, 8.85; I, 31.90; N, 3.54%.

8-(Benzyloxy)-5-chloro-7-[1,3]oxazolo[4,5-b]pyridin-2-ylquinoline (4)

A suspension of oxazolo[4,5-*b*]pyridine (**3**) (0.060 g, 0.500 mmol), 8-(benzyloxy)-5-chloro-7-iodoquinoline **2** (0.395 g, 1.000 mmol), Cs_2CO_3 (0.325 g, 1.000 mmol), $Pd_2(dba)_3$ (0.088 g, 0.100 mmol), and PPh_3 (0.508 g, 0.400 mmol) in CH_3CN (5 mL) was stirred and heated under reflux for 24 h. The mixture was then cooled, diluted with DCM (30 mL), and washed with sat. NH_4Cl (30 mL) and then sat. brine (50 mL). The aqueous layer was separated and extracted with DCM (2×50 mL). The combined organic layer was dried (Na_2SO_4) and filtered, and the filtrate evaporated under reduced pressure. The residue was purified by flash-column chromatography, eluting with 1:1 v/v ethyl acetate–hexane, to afford the product (0.271 g, 0.700 mmol, 70%) as colorless needles from ethyl acetate, mp 137–138°C. IR (solid) 3061, 3027, 2950, 2890, 1608, 1588, 1559, 1542, 1493, 1443, 1405, 1357, 1262, 1175, 1133, 1080, 1041, 963, 937, 907, 846, 782, 742, 725, 694, 669, 601, 578 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.1$ (1H, dd, $J = 4.1$ and 1.5, ArH), 8.62–8.65 (2H, m, ArH), 8.5 (1H, s, ArH), 7.77 (1H, dd, $J = 8.3$ and 1.35, ArH), 7.66 (2H, dd, $J = 8.3$ and 4.1, ArH), 7.3–7.6 (2H, m, ArH and ArH), 7.3–7.6 (4H, m, ArH), 5.6 (2H, s, CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.9$, 156.0, 155.0, 151.1, 147.5, 144.6, 143.6, 137.4, 133.8, 129.9, 129.1, 128.7, 128.6, 127.3, 127.1, 124.0, 120.9, 120.0, 118.8, 78.58. MS (ES^+): m/z (%) = 388 (^{35}Cl MH^+, 100), 390 (^{37}Cl MH^+, 30). HRMS m/z 388.0839 (calcd. for $C_{22}H_{15}ClN_3O_2$, 388.0847). Anal. calcd. for $C_{22}H_{14}ClN_3O_2 \cdot 0.25\ H_2O$: C, 67.35; H, 3.73; Cl, 9.04; N, 10.71. Found: C, 67.65; H, 3.50; Cl, 9.20; N, 10.65%.

5-Chloro-7-[1,3]oxazolo[4,5-b]pyridin-2-ylquinolin-8-ol (5)

Boron trichloride (1 M in DCM, 1.000 mL, 1.000 mmol) was added to a stirred solution of compound **4** (0.080 g, 0.206 mmol) in dry CH_2Cl_2 (4 mL) under N_2 via a syringe at -78°C over 5 min. The mixture was

stirred at 0°C for 1 h, diluted with DCM (5 mL), and quenched with ice water (20 mL). The organic layer was separated, dried (Na_2SO_4), and filtered, and the filtrate evaporated. Crystallization of the residue from 5% MeOH/DCM afforded the product **5** (0.056 g, 0.188 mmol, 91%) as orange-red needles, mp 168–170°C. IR (solid) 3307, 3005, 1629, 1599, 1552, 1503, 1448, 1369, 1267, 1138, 1089, 803, 761, 705, 589, 490 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 9.6$ (1 H, d, $J = 8.5$, ArH), 9.2 (1H, d, $J = 8.5$, ArH), 8.7 (1H, d, $J = 4.7$, ArH), 8.5 (1H, s, ArH), 8.3 (1H, dd, $J = 8.5$ and 4.7, ArH), 8.2 (1H, d, $J = 8.1$, ArH), 7.6 (1H, dd, $J = 8.1$ and 4.7, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 166.9$, 163.0, 153.1, 152.3, 147.8, 146.8, 142.0, 136.9, 132.4, 129.9, 126.7, 125.9, 125.7, 123.1, 122.5. MS (ES^+): m/z (%) = 298 (^{35}Cl MH+, 100), 300 (^{37}Cl MH^+, 30). HRMS m/z 298.0380 (calcd. for $C_{15}H_9ClN_3O_2$, 298.0378).

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REFERENCES

1. (a) Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Gonzales, E. Novel antimycobacterial benzoxazole alkaloids, from the West Indian sea whip *Pseudopterogorgia elisabethae*. *Org. Lett.* **1999**, *1*, 527–530; (b) Kobayashi, J.; Madono, T.; Shigemori, H. Nakijinol, a novel sesquiterpenoid containing a benzoxazole ring from an Okinawan sponge. *Tetrahedron Lett.* **1995**, *36*, 5589–5590.
2. For some examples, see (a) Rodriguez, I. I.; Rodriguez, A. D. Homopseudopteroxazole, a new antimycobacterial diterpene alkaloid from *Pseudopterogorgia elisabethae*. *J. Nat. Prod.* **2003**, *66*, 855–857; (b) Haansuu, J. P.; Klika, K. D.; Soderholm, P. P.; Ovcharenko, V. V.; Pihlaja, K.; Haahtela, K. K.; Vuorela, P. M. Isolation and biological activity of frankiamide. *J. Ind. Microbiol. Biotechnol.* **2001**, *27*, 62–66.
3. (a) Wipf, P. Synthetic studies of biologically active marine cyclopeptides. *Chem. Rev.* **1995**, *95*, 2115; (b) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. Ammonium chloride–promoted four-component synthesis of pyrrolo[3,4-b] pyridin-5-one. *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567; (c) Ikemoto, N.; Miller, R. A.; Fleitz, F. J.; Liu, J.; Petrillo, D. E.; Leone, J. F.; Laquidara, J.; Marcune, B.; Karady, S.; Armstrong, J. D.; Volante, R. P. Approaches to installing a *N*-gem-dimethylmethylene-2-oxazolyl group and application to the synthesis of a second-generation HIV protease inhibitor. *Tetrahedron Lett.* **2005**, *46*, 1867.

4. Sun, L. Q.; Chen, J.; Bruce, M.; Deskus, J. A.; Epperson, J. R.; Takaki, K.; Johnson, G.; Iben, L.; Mahle, C. D.; Ryan, E.; Xu, C. Synthesis and structure–activity relationship of novel benzoxazole derivatives as melatonin receptor agonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3799–3802.
5. Paramshivappa, R.; Kumar, P. P.; Subba Rao, P. V.; Srinivase Rao, A. Design, synthesis, and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 657–660.
6. Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1. *Bioorg. Med. Chem.* **2002**, *10*, 3997–4004.
7. Lopez-Tudanca, P. L.; Labeaga, L.; Innerarity, A.; Alonso-Cires, L.; Tapia, I.; Mosquera, R.; Orjales, A. Synthesis and pharmacological characterization of a new benzoxazole derivative as a potent 5-HT3 receptor agonist. *Bioorg. Med. Chem.* **2003**, *11*, 2709–2714.
8. (a) Chery, A. R.; Atwood, S. C.; Xillinas, E. M.; Gray, N. D.; Jones, D. W.; Mclean, A. C.; Barnham, J. K.; Moir, D. R.; Lim, T. J.; Beyreuther, K.; Zheng, H.; Tanzi, E. R.; Masters, L. C.; Bush, I. A. Treatment with a copper–zinc chelator markedly and rapidly inhibits β-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron.* **2001**, *30*, 665–667; (b) Treiber, C.; Simons, A.; Strauss, M.; Hafner, M.; Cappai, R.; Bayer, T. A.; Multhaup, G. Clioquinol mediates copper uptake and counteracts copper efflux activities of the amyloid precursor protein of Alzheimer's disease. *J. Biol. Chem.* **2004**, *279*, 51958–51964.
9. (a) Ding, W. Q.; Liu, B.; Vaught, J. L.; Yamauchi, H.; Lind, S. E. Anticancer activity of the antibiotic clioquinol. *Cancer Res.* **2005**, *65*, 3389–3395; (b) Vaira, M. D.; Bazzicalupi, C.; Orioli, P.; Messori, L.; Bruni, B.; Zatta, P. Clioquinol, a drug for Alzheimer's disease specifically interfering with brain metal metabolism: Structural characterization of its zinc(II) and copper(II) complexes. *Inorg. Chem.* **2004**, *43*, 3795–3797.
10. Fedor, A. Z. Unprecedentedly mild direct Pd-catalyzed arylation of oxazolo[4,5-b]pyridine. *Tetrahedron Lett.* **2006**, *47*, 2929–2932.
11. (a) Zouhiri, F.; Danet, M.; Benard, C.; Normand-Bayle, M.; Mouscadet, J.; Leh, H.; Thomas, C. M.; Mbemba, G.; Angelo, J.; Desmaele, D. HIV-1 replication inhibitors of the styrylquinoline class: Introduction of an additional carboxyl group at the C-5 position of the quinoline. *Tetrahedron Lett.* **2005**, *46*, 2201–2205; (b) Gillespie, J. P.; Amoros, L. G.; Stermitz, F. R. Synthesis of fagaronine, an anticancer benzophenanthridine alkaloid. *J. Org. Chem.* **1974**, *39*, 3239–3241.
12. Doise, M.; Dennin, F.; Blondeau, D.; Sliwa, H. Synthesis of novel heterocycles: Oxazolo[4,5-b]pyridines and oxazolo[4,5-d]pyrimidines. *Tetrahedron Lett.* **1990**, *31*, 1155–1156.