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Palladium-Mediated Benzylation of Dimetalated 1-Butylindole-3-carboxylic Acid

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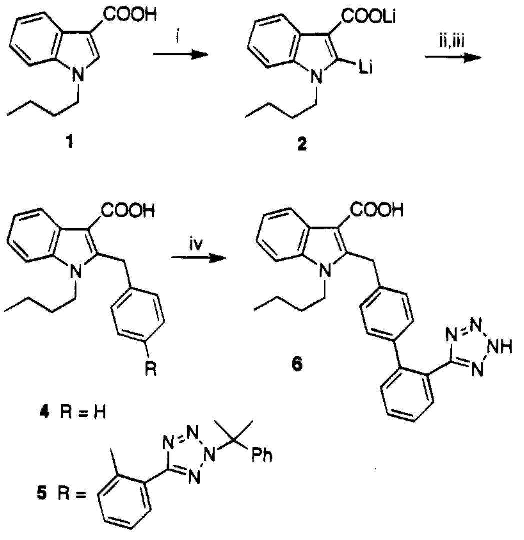
As a result of a medicinal chemistry program, multikilogram quantities of the 2-indolylmethyl biphenylyltetrazole **6**, a novel CNS agent, were required for advanced pharmacological evaluation. Our initial synthesis of **6**, which involved coupling of the dilithio species **2** with a biphenyl aldehyde followed by deoxygenation of the resulting benzylic alcohol,[1] was not amenable to scale-up. Thus we desired a method for direct coupling of **2** with the protected tetrazolyl biphenylylmethyl halide **3**.[2] In this Note, we describe the realization of this coupling using a palladium-mediated process that has been successfully carried out on a 25−30 kilogram scale.

Dilithio species **2** was readily prepared by treatment of 1-butylindole-3-carboxylic acid (**1**) with 2 equiv of *n*-BuLi in THF.[3] However, in model studies, treatment of **2** with benzyl bromide failed to give the desired coupling product **4** as starting acid **1** was recovered in quantitative yield along with benzyl bromide and bibenzyl. This result was in accord with the reported failure of the dilithiated 1-methyl analogue to couple with benzyl bromide.[3] Failure to alkylate with benzyl halides is a phenomenon observed with a number of other *ortho*-lithiated deriviatives including furan-[4] and thiophene-3-carboxylic acids.[5]

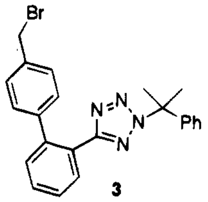
Scheme 1[a]



[a] Reagent and conditions: (i) *n*-BuLi, THF; (ii) ZnC12; (iii) BnBr or **3**, $Pd(PPh_3)_4$; (iv) $HSCH_2CO_2Et$, $BF_3{\cdot}OEt$, MeCN.

Negishi et al. reported that phenylzinc chloride coupled efficiently with benzyl bromide in the presence of $Pd(PPh_3)_4$.[6] Benzylation of 2-furylzinc chloride under these conditions has also been reported.[7] Thus we were prompted to study the benzylation of organozinc species derived from transmetalation of **2**.[8] Indeed treatment of dilithio species **2** with 0.5 equiv of $ZnCl_2$ followed by 1−2 mol % of $Pd(PPh_3)_4$ and 1 equiv of benzyl bromide afforded coupling product **4** in 77% yield (Scheme 1). This coupling reaction proceeded with as little as 0.1 equiv of $ZnCl_2$, albeit with slightly reduced efficiency,[9] implying that the zinc halide participates in a catalytic cycle. Control experiments indicated that **2** did not couple with benzyl bromide in the presence of $Pd(PPh_3)_4$, nor did the presumed organozinc intermediate couple in the absence of the palladium catalyst.

When biphenylmethyl bromide **3**[2] was used in place of benzyl bromide, the coupling product **5** was isolated in 80−90% yield after crystallization. The adaptability of this process to a large scale was demonstrated in pilot plant runs that produced 8.1 and 28.5 kg of **5** in yields of 85% and 80%, respectively. To complete the synthesis of target compound **6**, removal of the tetrazole protecting group from **5** was accomplished in over 90% yield on a multikilogram scale by treatment with boron trifluoride etherate and ethyl thioglycolate in acetonitrile. The deprotection could also be carried out on a small scale (<10 g) by transfer hydrogenation (Pd−C, ammonium formate in methanol), but this procedure was not readily adaptable to a larger scale.



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Although the scope of the palladium-mediated benzylation of arylzinc species derived from similar directed lithiation/transmetalation protocols remains to be demonstrated,[10] the process is clearly useful for effecting the benzylation of 1-alkylindole-3-carboxylic acids.[11] It is of interest to note that palladium-catalyzed acylation of organozincs, obtained from transmetalation of organo-

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(2) Clark, R. D.; Fisher, L. E.; Flippin, L. A.; Martin, M. G.; Stabler, S. R. United States Patent 5,412,102 (1995); *Chem. Abstr.* **1995**, in press.

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(5) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 791.

(6) Negishi, E.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, 2715.

(7) Pelter, A.; Rowlands, M.; Clements, G. *Synthesis* **1987**, 51.

(8) Arylation and heteroarylation of 2-indolylzinc derivatives has been reported: (a) Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. *Heterocycles*, **1993**, *36*, 941. (b) Amat, M.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1993**, *34*, 5005.

(9) In the presence of 10 mol % $ZnCl_2$, conversion of dilithio species **2** to **4** was determined to be 75% by NMR analysis of the crude product, whereas conversion was ca. 95% with 50 mol % $ZnCl_2$ (16 h reaction time in both cases).

(10) The dilithio species generated from furan-3-carboxylic acid and from *N*-(*tert*-butoxycarbonyl) aniline, neither of which couple with benzyl halides under standard conditions, were subjected to the protocol described above for benzylation of **2**; however, in neither case was benzylation observed.

(11) Benzylation of 1-methylindole-3-carboxylic acid proceeded similarly to benzylation of **1**.

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lithiums obtained by directed metalation, has recently been reported.[12]

Experimental Section

2-Benzyl-1-butyl-1*H*-indole-3-carboxylic acid (4). A solution of **1**[13] (543 mg, 2.5 mmol) in THF (20 mL) was cooled to −20 °C and *n*-butyllithium (3.1 mL of 1.6 M solution in hexane, 5 mmol) was added. The resulting solution was stirred at −20 °C for 20 min, and zinc chloride solution (Aldrich, 1.25 mL of 1 M in ether, 1.25 mmol) was added. After 5 min, benzyl bromide (0.3 mL, 2.5 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with CH_2Cl_2 and washed with dilute aqueous HCl. The CH_2Cl_2 was washed with brine, dried (Na_2SO_4), and evaporated to a solid residue. Recrystallization from EtOAc−hexane afforded 594 mg (77%) of **4** as a white solid: mp 176−178 °C; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, J = 7.2 Hz), 1.35 (m, 2H), 1.86 (m, 2H), 3.97 (t, 2H, J = 7.7 Hz), 4.74 (s, 2H), 7.14−7.30 (m, 8H), 8.29 (m, 1H); IR (KBr) 3433 (br), 1655 cm^{-1}; LRMS (EI) m/z (relative intensity) 307 (M$^+$, 100). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.89; H, 6.88; N, 4.58.

1-Butyl-2-[2′-[2-(1-methyl-1-phenylethyl)-2*H*-tetrazol-5-yl]-biphenyl-4-ylmethyl]-1*H*-indole-3-carboxylic acid (5). A 400 L reactor was charged with **1** (15.3 kg, 70.3 mol) and THF (160 L). The solution was cooled to −5 °C, and *n*-butyllithium (64.7 L of 1.6 M in hexane, 148 mol) was added at such a rate that the internal temperature did not exceed 7 °C. The mixture was stirred at 0 °C for an additional h, and a solution of zinc chloride (Alfa−Johnson Matthey, 5.6 kg, 41 mol) in THF (48 L) was added at such a rate that the internal temperature did not exceed 5 °C. After 1 h at 0 °C, a solution of bromide **3** (29 kg, 67 mol) in THF (64 L) and a solution of $Pd(PPh_3)_4$ (1.6 kg, 1.4 mol) in THF (26 L) were added sequentially. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. A solution of 85% phosphoric acid (13.5 kg) in water (50 L) was added, the layers were separated, and the organic layer was treated with Celite (3.4 kg) and aqueous NaOH (5 kg of NaOH in 55 L of water). The mixture was filtered, brine (53 L) was added, and the layers were again separated. The organic layer was filtered through a 1 μm cotton cartridge filter to remove a black residue (probably palladium). Distillation in vacuo, with gradual replacement of solvent with 135 L of EtOAc and 210 L of MeOH followed by volume reduction to ca. 180 L, resulted in formation of crystals. The distillation was halted and the mixture was stirred at −5 °C. The solid was collected by filtration and washed with MeOH (20 L). The filtrate was concentrated to ca. 85 L and filtered to a solid which was combined with the original solid to afford a total of 28.5 kg (80%) of **5** (99.6% pure by HPLC): mp 142−144 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.26 (m, 2H), 1.50 (m, 2H), 1.92 (s, 6H), 3.97 (t, 2H, J = 7.5 Hz), 4.73 (s, 2H), 6.86 (m, 2H), 7.05 (s, 4H), 7.10 (m, 3H), 7.25 (m, 3H), 7.36 (m, 1H), 7.45 (m, 2H), 7.85 (m, 1H), 8.30 (m, 1H); IR (KBr) 3435 (br), 1651 cm^{-1}; LRMS (EI) m/z (relative intensity) 569 (M$^+$, 70). Anal. Calcd for $C_{36}H_{35}N_5O_2$: C, 75.90; H, 6.19; N, 12.29. Found: C, 75.67; H, 6.11; N, 12.13.

1-Butyl-2-[2′-(2*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1*H*-indole-3-carboxylic Acid (6). A suspension of the protected tetrazole **5** (10 g, 18 mmol) in acetonitrile (100 mL) was heated under reflux until all solid had dissolved (ca. 10 min). The resultant solution was cooled to 25 °C and methyl thioglycolate (6.1 g, 68 mmol) and boron trifluoride etherate (8.7 mL, 70 mmol) were added. After being stirred for 3 h, the mixture was cooled in an ice-bath and treated successively with toluene (30 mL), 15% NaOH (73 mL), and 3 M HCl (70 mL). The precipitate was collected by filtration, and the filtercake was washed water and dried in vacuo at 75 °C for 12 h to afford 7.2 g (91%) of **6** as a white solid (97.3% pure by HPLC): mp 211−214 °C; ^{1}H NMR (DMSO-d_6) δ 0.77 (t, 3H, J = 7.1 Hz), 1.15−1.36 (m, 4H), 4.06 (t, 2H, J = 7.8 Hz), 4.70 (s, 2H), 7.01 (d, 2H, J = 8.25 Hz), 7.14 (d, 2H, J = 8.25 Hz), 7.14−7.22 (m, 2H), 7.44−7.68 (m, 5H), 8.06 (m, 1H), 12.20 (br s, 1H); IR (KBr) 3410 (br), 1650 cm^{-1}; LRMS (EI) m/z (relative intensity) 451 (M$^+$, 60). Anal. Calcd for $C_{27}H_{25}N_5O_2$: C, 71.84; H, 5.54; N, 15.52. Found: C, 72.13; H, 5.73; N, 15.23.

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(13) Acid **1** was prepared according to the procedure described in reference 3 for 1-methylindole-3-carboxylic acid.