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New Heck coupling strategies for the synthesis of paullone and dimethyl paullone

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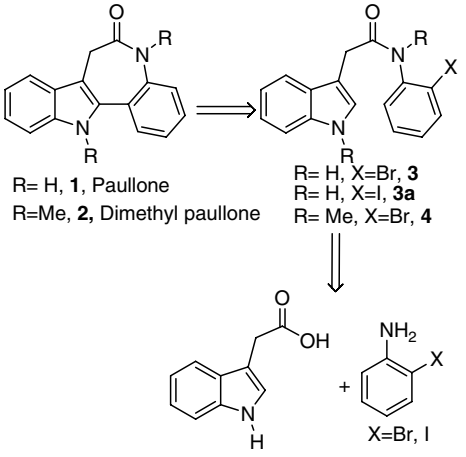
Abstract—The short total synthesis of paullone (**1**) and dimethyl paullone (**2**) via a novel palladium-catalyzed intramolecular coupling using the *o*-bromo- and *o*-iodo anilides of indoles (**3** and **3a**) and *N*-methyl indole **4** is described.

Paullones[1] are a series of structures from 7,12-dihydroindolo[3,2-*d*]benzazepin-6(5*H*)-ones,[2] which constitute a class of CDK inhibitors.[3] These cyclin-dependent kinases[2] (CDKs) are a family of serine–threonine kinases that play a major role in cell cycle division. In a wide variety of human tumors and tumor cell lines, CDK-related mechanisms are deregulated.[4] Synthetic CDK-inhibitors have been studied as potential candidates for treating neoplastic diseases.[5] In addition, paullones are potent inhibitors of glycogen synthase kinase-3B (GSK-3B) and neuronal CDK5/p25.[5] These latter two enzymes cause hyperphosphorylation of the microtubule-binding protein tau, a feature observed in the brains of patients with Alzheimer's disease.[3] The dual specificity of paullones makes them potentially very useful agents for the treatment of neurodegenerative and proliferative disorders.

Paullone (**1**) has been synthesized by the reaction of anthranilic acid ethyl ester with ethyl succinoyl chloride to yield an amide, on which Dieckmann condensation was performed followed by a Fischer indole synthesis.[1a] In addition, **1** can be obtained from 1,4-naphthoquinone by the Schmidt reaction followed by catalytic reduction and indolization.[6] **1** has also been prepared by a synthetic strategy involving a palladium-catalyzed borylation–Suzuki coupling reaction sequence.[7]

Here, we describe a short route for constructing paullone (**1**) and dimethyl paullone (**2**) via a novel intramolecular cyclization of the indole derivatives **3**, **3a** and **4**, respectively (Scheme 1).

The indole derivative **3** and **3a**[8] were easily obtained by treating 3-indolylacetic acid and *o*-bromo or *o*-iodoaniline with a solution of DCC in CH_2Cl_2. Based on the precedent that one generalized intramolecular



Scheme 1.

Keywords: Indole; Cyclization; Free radical; Palladium; Intramolecular; Paullones.
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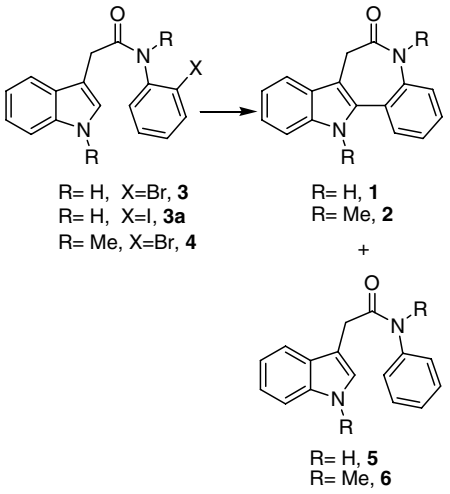

Scheme 2.

reaction had been used to synthesize heterocyclic compounds on treatment with tributyltin hydride in the presence of lauroyl peroxide (LP) or AIBN,[9] we decided to perform the cyclization via these conditions. Only the reductive dehalogenation product **5**[10] was obtained under these and related conditions rather than the desired product **1** (Scheme 2).

These negative results led us to explore an intramolecular palladium-catalyzed C-arylation of the aryl halide **3** and **3a** in the presence of a base. Whereas the use of the standard alkali metal base K_3PO_4 produced only the reduced compound **5** (Table 1, entry 1), MgO, which is reported to be the optimum base for the arylation of indole and other (NH)-heteroarenes,[11] gave paullone (**1**) in two steps as the only product, albeit only in ca 9, 10% yield and the main product in 70% yield (Table 1, entries 2–4). Bremner and Sengpracha achieved a total synthesis of **1** in eight steps (1.27% yield) using as key step a free radical cyclization of an iodoacetamide derivative.[12] Given the fact that there are two NH groups in the starting material, it is noteworthy that no N-arylation products were detected in the reaction mixture. Furthermore, the starting material which had not been consumed could be recovered in high yield, and thus in principle is recyclable. We then decided to test both the radical and the palladium based methods for the intramolecular cyclization of the bis-*N*-methylated compound **4**. After some optimization (base, solvent, temperature), **4**[13] was prepared from **3** in 82% yield with powdered KOH and methyl iodide in DMSO[14] solution. The best result for the cyclization via free radicals[15] was obtained with *n*-Bu_3SnH in the presence of AIBN at 80 °C for 4 h, which yielded the desired compound **2** (12%) in three steps and the reduced compound **6** (60%, entry 5).

Table 1. Cyclization reactions with Palladium

Entry	Substrate	Conditions[a] (mol)	Products (%)
1	**3**	K_3PO_4 (1.4)	**5** (60) **3** (28)
2	**3**	MgO (1.4)	**1** (9) **3** (88)
3	**3**	MgO (2.8)	**1** (10) 3 (78)
4	**3a**	MgO (2.8)	**1** (70) **5** (18)
5	**4**	*n*-BuSnH (1) AIBN (1)	**2** (12) **6** (60)
6	**4**	K_3PO_4 (1.4)	**2** (46) **6** (36)
7	**4**	K_3PO_4 (1.2)	**2** (33) **6** (20)
8	**4**	Cs_2CO_3 (1.4)	**2** (86) **6** (13)

[a] All yields were determined by GC–MS. $Pd(OAc)_2$ was used in 0.1 mol. Solvents used: DMF (**1**–**4**, **6** and **8**), DMA (**7**) and C_6H_6 (**5**); temperature: 130 °C except **5** 80 °C. Time: 4 h (**5**); 24 h (**1**–**4**); 30 h (**6**–**8**).

For the palladium catalyzed cyclization[16] with the common base K_3PO_4, we also found the two competitive processes: the desired cross-coupling and the reduced compound formation (entries 6 and 7). However, using Cs_2CO_3 as a base[17] in simple conditions we improve the intramolecular palladium-catalyzed C_2-arylation, obtaining an excellent yield (86%) in three steps of the desired dimethyl paullone (**2**), with low catalyst loading in DMF as a solvent and 13% yield of the reduced compound **6** (entry 8). The synthesis of **2** using the iododerivatives, $Pd(OAc)_2$, PPh_3 and $AgCO_3$, was accomplished under similar conditions by Benoit and co-workers.[18]

In conclusion, this investigation presents a new, short, practical method by which (NH **3**, **3a** and NMe **4**)-indoles may be intramolecularly cyclized to paullone **1** and dimethyl paullone **2** with low catalyst loading, under Heck reaction conditions. Using free radicals we get **2** and the reduced compounds **5**[10] and **6**[19] were the major products. The application of the present method carries the potential of also being extended to several other products syntheses.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.118.

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13. Selected spectral data. Compound **4**: IR (film): 3054, 3024, 1666, 1651, 1583, 1476, 1373, 129, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) d 7.69 (dd, $J = 1.5/7.8$ Hz, 1H), 7.34–7.14 (m, 4 H), 7.04 (d, $J = 1.2$ Hz, 1H), 7.01 (t, $J = 1.2$ Hz, 1H), 6.99 (d, $J = 1.2$ Hz, 1H), 6.85 (s, 1H), 3.71 (s, 3H), 3.51 (br s, 1H), 3.50 (br s, 1H), 3.22 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) d 166.10, 142.92, 136.70, 133.80, 130.14, 129.63, 128.78, 127.78, 123.58, 121.39, 118.88, 118.79, 108.96, 107.50, 36.10, 32.57, 30.85. MS, *m*/*z* (%) M^+ 356 (42), M^++2 358 (41), 144 (100), 143 (27). HRMS *m*/*z* for $C_{18}H_{17}ON_2Br$. Calcd: 356.0524, found: 356.0524. Compound **2**: IR (film): 1660, 1469, 1371, 1115, 742. ^1H NMR (400 MHz, $CDCl_3$) d 7.74 (dt, $J = 0.8/0.8/8$ Hz, 1H), 7.55 (dd, $J = 2/8$ Hz, 1H), 7.48–7.28 (m, 5H), 7.2 (t, $J = 7.2$ Hz, 1H), 3.96 (d, $J = 14.4$ Hz, 1H), 3.90 (s, 3H), 3.35 (s, 3H), 3.06 (d, $J = 14$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 172.82, 141.69, 139.17, 133.66, 128.51, 127.94, 125.59, 124.98, 124.62, 124.22, 122.75, 119.97, 118.68, 112.31, 109.68, 37.61, 32.24, 31.75. MS, *m*/*z* (%) M^+ 276 (75), 261 (68), 247 (100), 232 (20), 117 (19). HRMS *m*/*z* for $C_{18}H_{16}ON_2$. Calcd: 276.1263, found: 276.1264.
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