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Palladium Catalyzed Synthesis of Annelated Indoles

Alan P. Kozikowski* and Dawei Ma

Neurochemistry Research, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, Florida 32224

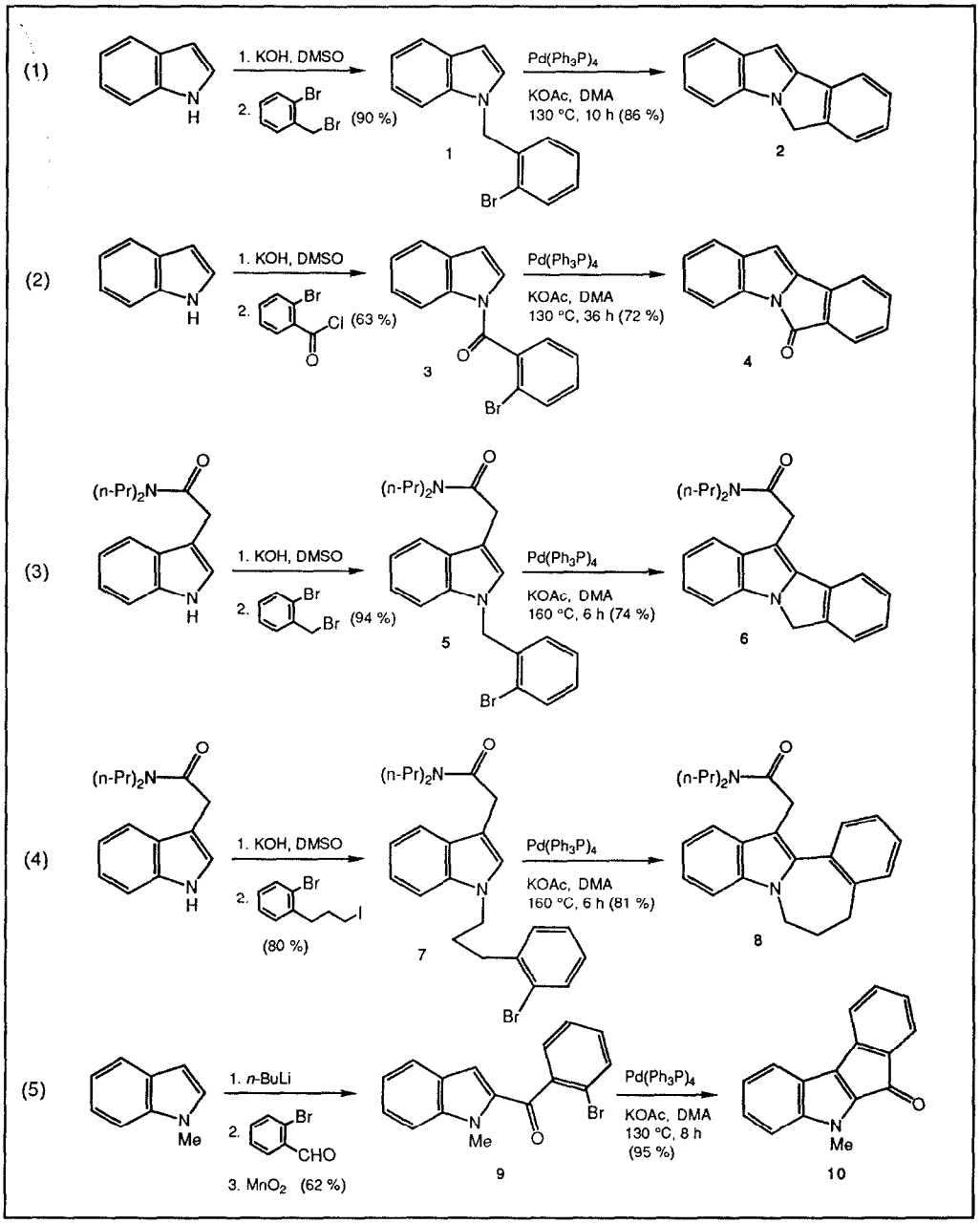
Abstract: *The synthesis of polycyclic indoles is shown to be accomplished readily by the palladium catalyzed intramolecular cyclization of bromoaryl bearing indoles.*

During our efforts to develop selective ligands for the peripheral type benzodiazepine receptors (PBR), a receptor system now known to be linked to steroidogenesis[1], the need arose to construct certain annelated derivatives of indole. While Itahara has reported the preparation of 6-oxo-6*H*-isoindolo[2,1-*a*]indoles by intramolecular dehydrogenation with palladium(II) acetate [2], the yields obtainable by this method are generally variable (47-7%), and the ability of this method to accommodate the formation of larger ring sizes appears questionable. A further drawback of the method stems from the necessity to use 0.5 equivalents of the expensive palladium reagent.

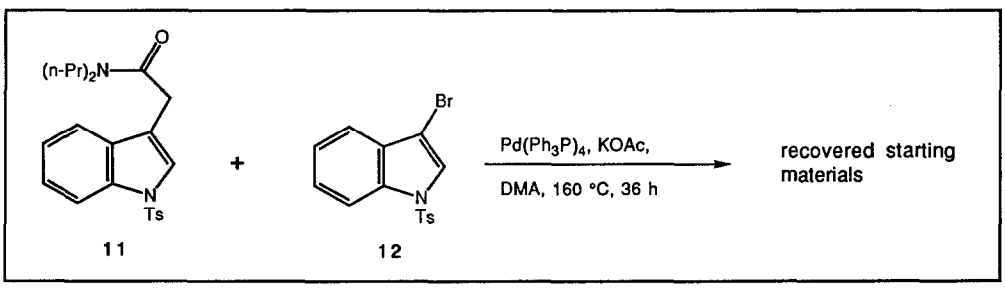
Consequently, we have investigated the use of tetrakis(triphenylphosphine)palladium(0) to catalyze the intramolecular cross-coupling of an indole with an aryl bromide. The feasibility of the method was tested employing N-(*o*-bromobenzyl)indole (**1**) as substrate. A mixture of the indole, $(Ph_3P)_4Pd$, and KOAc in dimethylacetamide (DMA) was heated at 130 °C for six hours. The solvent was then removed, and the residue was chromatographed to provide the desired tetracycle **2** in 86% yield. On reacting the N-(*o*-bromobenzoyl)indole (**3**), prepared as shown in Table 1, under similar conditions, a 72% yield of the polycycle **4** was isolated. This yield is to be contrasted with the 47% isolated yield reported for the preparation of **4** by the $Pd(OAc)_2$ method of reference 1.

Having established the feasibility of the method, we now applied this cyclization protocol to the preparation of the peripheral benzodiazepine receptor-specific ligands which differ from **1** by the presence of an acetamide moiety at the C-3 position of the indole nucleus. The palladium catalyzed cyclization reaction proceeded readily in cases where either a five-membered or seven-membered ring was formed[4]. Compound **5** was transformed to polycycle **6** in 74% yield, while **7** provided **8** in 81% yield.

Palladium Catalyzed Intramolecular Cyclization Route to Polycyclic Indoles.



While the previous four examples result in annelation of a new ring to the N(1)-C(2) positions of the indole nucleus, we also found the method to work equally well in the case where a new ring is affixed to the C(2)-C(3) positions of the indole nucleus. The starting compound **9** was prepared by metalation of N-methylindole at its 2-position and trapping of the resulting anion by *o*-bromobenzaldehyde followed by oxidation with manganese dioxide[5]. Palladium catalyzed cyclization of this intermediate provided the tetracycle **10** in 95% yield. The structural resemblance of **10** to ellipticine is suggestive of yet another route to this biologically active natural product[6]. At present, we have found this coupling method to fail only when it was attempted in the **intermolecular** sense. For example, the reaction of **11** and **12** led only to the recovery of starting materials.



In summary, the palladium catalyzed cyclization methodology works exceedingly well with indoles as substrates and provides a remarkably facile entry to conformationally constrained PBR-specific ligands. While the biology of these new ligands will be reported in detail in separate publications, it is interesting to note that both compound **6** and its more flexible counterpart **8** display high affinity for the peripheral benzodiazepine receptor[7].

General Procedure: A mixture of the indole substrate (8.8 mmol), $Pd(Ph_3P)_4$ (0.44 mmol), and potassium acetate (8.8 mmol) in 120 mL of N,N-dimethylacetamide was heated at 160 °C for 6 h. The solvent was then removed under reduced pressure at 80 °C, and the residue was chromatographed on silica gel to provide the cyclization product.

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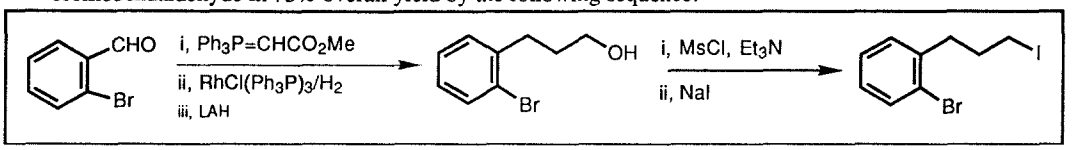
References and Notes.

1. V. Papadopoulos, A. G. Mukhin, E. Costa, and K. E. Krueger, *J. Biol. Chem.* **1990**, 265, 3772.
2. T. Itahara, *Synthesis* **1979**, 151; T. Itahara, *Chem. Lett.* **1982**, 1151.

3. For the cross-coupling reaction of N-substituted indoles with chloropyrazines, see Y. Akita, Y. Itagaki, S. Takizawa and A. Ohta, *Chem. Pharm. Bull.* **1989**, 37, 1477.

4. The 3-(*o*-bromophenyl)propyl iodide used in the synthesis of **8** was prepared from *o*-bromobenzaldehyde in 75% overall yield by the following sequence:



5. (a) F. E. Ziegler and E. B. Spitzner, *J. Am. Chem. Soc.* **1973**, 95, 7146; (b) D. A. Shirley and P. A. Roussel, *ibid.*, **1953**, 75, 375.

6. G. W. Gribble, *The Alkaloids* **1990**, 39, 239.

7. Unpublished data from A. Guidotti *et al.*, Fidia-Georgetown Institute for the Neurosciences, 1991.

8. Spectral data for compounds **2**, **6** and **8** follow:

2) IR (KBr) 3043, 1579, 1467, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, 1H), 7.66 (d, 1H), 7.45 (d, 1H), 7.28-7.29 (m, 3H), 7.22 (dd, 1H), 7.10 (dd, 1H), 6.63 (s, 1H), 5.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 144.0, 141.8, 133.9, 133.1, 132.1, 128.2, 127.1, 123.6, 121.8, 121.6, 120.9, 119.7, 109.3, 91.3, 48.5; mass spectrum m/z 205 (M^+), 176, 151, 102, 75, 63.

6) IR (KBr) 3046, 1635, 1468, 1425 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, 1H), 7.71 (d, 1H), 7.38-7.47 (m, 2H), 7.26-7.34 (m, 2H), 7.14 (dd, 1H), 7.09 (dd, 1H), 5.06 (s, 2H), 4.07 (s, 2H), 3.19-3.28 (m, 4H), 1.36-1.55 (m, 4H), 0.79 (t, 3H), 0.70 (t, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.9, 141.8, 141.1, 133.6, 133.1, 132.2, 128.3, 126.9, 123.5, 122.0, 121.8, 119.9, 119.5, 109.2, 100.3, 49.9, 48.3, 47.9, 31.8, 22.2, 20.9, 11.4, 11.2; mass spectrum m/z 346 (M^+), 218, 159, 128, 109, 99, 84, 69, 55.

8) IR (KBr) 3011, 2953, 1633, 1450, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, 1H), 7.51 (m, 1H), 7.34-7.48 (m, 4H), 7.21 (dd, 1H), 7.08 (dd, 1H), 4.11-4.21 (m, 2H), 3.89 (s, 2H), 3.01 (m, 2H), 2.92 (m, 2H), 2.63 (t, 2 H), 2.25 (m, 2H), 1.36-1.58 (m, 4H), 0.81 (t, 3H), 0.58 (t, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.0, 139.1, 138.2, 135.7, 132.1, 129.6, 129.4, 128.6, 127.8, 126.7, 121.9, 120.1, 119.2, 108.4, 106.0, 49.6, 47.9, 40.5, 31.2, 31.0, 30.8, 22.3, 21.0; mass spectrum m/z 374 (M^+), 246, 217, 128, 115, 86.

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