Benzenoid Ring Functionalization of Indoles and Tryptophols *via* Combined Directed *Ortho* Metalation–Cross Coupling Methodology

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We report new strategies for the regiospecific construction of 4-, 5-, and 6- substituted indoles and tryptophols **2** by adaption of directed *ortho* metalation (DoM)[1,2] and transition metal catalyzed cross coupling[1,3] reactions on *N,N*-diethylindole 5-*O*-carbamate **1** (Scheme 1). While the elaboration of the tryptamine side chain is readily effected by conventional means, versatile methods for the introduction of functionality into the benzene ring are lacking and usually involve classical electrophilic substitution or prior incorporation of substituents in *de novo* indole ring construction.[4] Recent years have witnessed rapid advances in research on serotonin (5-hydroxytryptamine, 5-HT) and melatonin, neurotransmittors involved in a broad range of physiological processes.[5] The remarkable heterogeneity of 5-HT receptors[6] and the potential for the discovery of new pharmacological and therapeutic agents[7] have served as powerful stimuli for the synthetic modification of indole and tryptamine derivatives.[8] The preliminary results reported herein constitute the first direct and general methodology for the modification of the benzenoid moiety of indoles which may have value in the development of new synthetic neurotransmitters and in pharmacological studies related to 5-HT receptors.

On the basis of previous studies,[4b,9,10] we anticipated that a bulky *N*-silicon group in **1** would prevent 2-deprotonation[2] and allow development of conditions for benzene ring metalation. In the event, treatment of **3**[11,12] (Scheme 2) under standard metalation conditions[13] followed by quench with MeI gave **4a**[12] (Table 1) in quantitative yield. Extension to other electrophiles indicates the generality of this process: functional carbon electrophiles at various oxidation states (entries 1–4), some of which are valuable for lysergic acid synthesis,[14] NH_2^+ and OH^+ synthons (entries 5 and 6),[15] halogens (entries 8 and 9), sulfur (entry 10),[16] and silicon (entry 11) electrophiles are introduced in modest to excellent yields.

Following the concept of silicon protection for kinetically reactive anionic sites previously established in our

Scheme 1

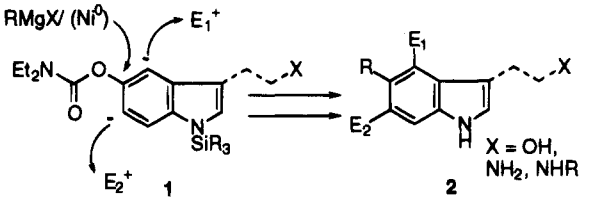
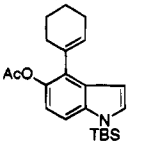
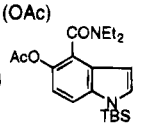


Table 1. Synthesis of 4-Substituted 5-*O*-Indole Carbamates

Entry	Starting Material	E⁺ or Conditions[a]	Product (E)	Yld, %[b]
1	**3**	MeI	**4a** (Me)	99
2	**3**	DMF	**4b** (CHO)[c]	96
3	**3**	A	**4c** 	50
4	**3**	$ClCO_2Et$	**4d** (CO_2Et)	43
5	**3**	B	**4e** (NHAc)	47
6	**3**	C	**4f** (OAc)	59
7	**3**	D	**4g** 	25
8	**3**	C_2Cl_6	**4h** (Cl)	90
9	**3**	I_2	**4i** (I)	79
10	**3**	$^tBuSSO_2Ph$	**4j** (tBuS)	77
11	**3**	TMSCl	**4k** (TMS)	90
12	**4k**	MeI	**5a** (Me)	63
13	**4k**	I_2	**5b** (I)	63

[a] A: (1) cyclohexanone, (2) AcOH/THF, (3) Ac_2O/Et_3N//DMAP (cat). B: (1) TsN_3, (2) EDTA, (3) $Pd/C/H_2$, (4) Ac_2O. C: (1) $MgBr_2$, (2) camphor sulphonyl oxaziridine, (3) AcOH, (4) Ac_2O/Et_3N. D: (1) ^tBuOOLi, (2) Ac_2O/Et_3N. [b] Yields represent purified (chromatographed) materials. [c] Quenched at −78 °C with AcOH/THF to avoid carbamate loss; see ref 13.

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(8) For example, synthetic work has focused on the preparation of serotonin mimics exhibiting locked conformations or bearing additional functionality to probe receptor site selectivity: Swain, C. J.; Baker, R.; Kneen, C.; Herbert, R.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G. I.; Beer, M.; Stanton, J.; Watling, K.; Ball, R. G. *J. Med. Chem.* **1992**, *35*, 1019. See also: Varie, D. L. *Tetrahedron Lett.* **1990**, *31*, 7583 and references cited therein. Varie, D. L. National Meeting of the American Chemical Society, Washington, D.C., Aug 1994; Abstract ORG-98.

(9) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *41*, 3324.

(10) Iwao, M. *Heterocycles* **1993**, *36*, 29.

(11) Compound **3** was routinely prepared on 20 gram scale as follows: commerical 3-methyl-4-nitrophenol was converted (1. NaH/DMF; 2. Et_2NCOCl, 92%) into the corresponding carbamate which was subjected to the Leimgruber–Batcho synthesis: 1. $(MeO)_2CNMe_2$/DMF; 2. 10% Pd/C/toluene/H2, 1 atm (*Org. Synth.* **1985**, *63*, 214) and silylation (NaH/TBSCl) to afford the product in 63% overall yield without chromatography.

(12) Salient NMR data. Compound **3:** ^1H NMR δ 7.44 (d, J = 9.0, 1H, H7), 7.34 (d, J = 2.4, 1H, H4), 6.92 (dd, J = 9.0, 2.4, 1H, H6). Compound **4a:** ^1H NMR δ 7.21 (d, J = 8.8, 1H, H7), 6.87 (d, J = 8.8, 1H, H6). Compound **12a:** ^1H NMR δ 7.35 (s, 1H, H4), 7.99 (s, 1H, H7).

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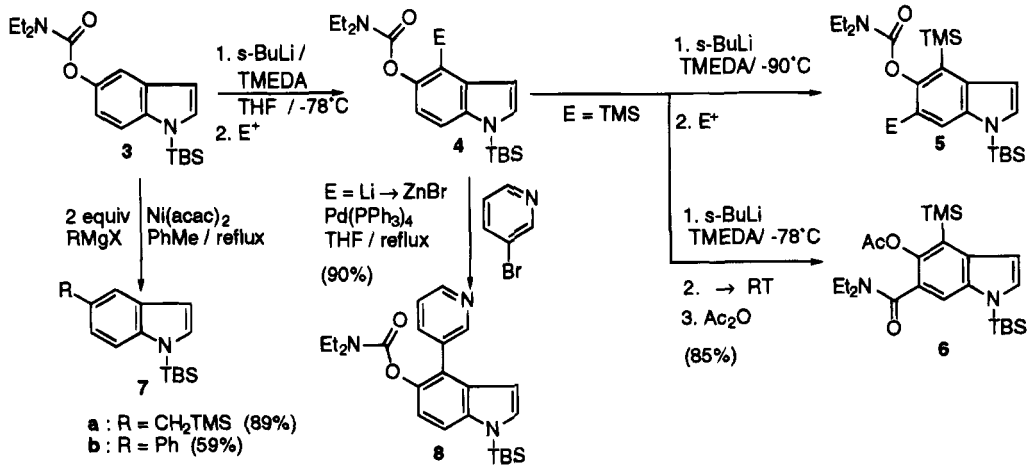
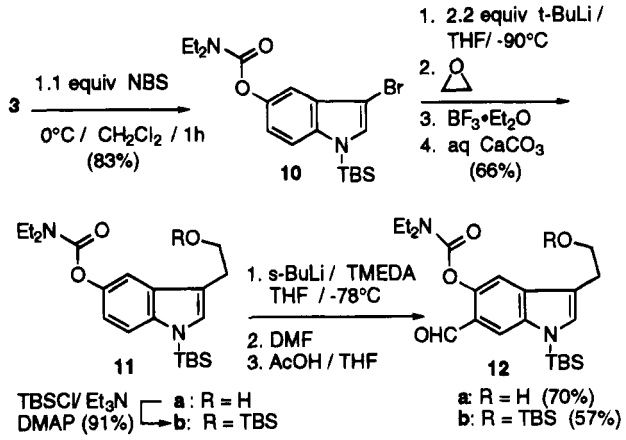
0022-3263/95/1960-1484$09.00/0

Scheme 2



Scheme 3



laboratories,[17] the carbamate **4**, E = TMS (Scheme 2), was subjected to the identical metalation conditions except at lower temperatures to avoid the anionic *ortho*-Fries rearrangement[13] and quenched with electrophiles to give 6-substituted products **5a-b** (Table 1, entries 12 and 13), thus demonstrating the viability of selective 4- and 6-substitution. In an attempt to hydroxylate **3**, the anionic Fries was observed to give, after acylation, **4g** (entry 7). Under standard conditions[13] followed by acylation, **4k** afforded **6**. Both products may be amenable to further metalation chemistry.

In order to demonstrate modern transition metal catalyzed cross coupling in which the indole derivative acts as the organometallic partner, the 4-lithio species **4**, E = Li (Scheme 2), was transmetalated with $ZnBr_2$ following the excellent Negishi procedure[18] and coupled with 3-bromopyridine to give compound **8** in very good yield.[19] Successful cross coupling of iodinated products **4i** and **5b** (entries 9 and 13) may also be anticipated.

The recently established[20] Grignard reagent–aryl *O*-carbamate cross coupling reaction was adapted to demonstrate viability of C-5 substitution. Thus, compound **3** was converted into **7a** and **7b** in good yields.[21]

In order to demonstrate synthetically advantageous metalation of tryptophol derivatives, the metalation–formylation of the 5-*O*-carbamate **11a** (Scheme 3) and its side chain protected derivative **11b**, prepared via **10** from the parent indole **3**, was explored. Surprisingly, both **11a** and **11b** led, upon DMF quench, to the formation of 6-formylated products, **12a** and **12b**, respectively. This result which is perhaps associated with side-chain conformational effects[22] suggests potential for direct modification of tryptophols and tryptamines.

In conclusion, this work constitutes the first demonstration of a general DoM approach for functionalization of the benzenoid portion of indoles and tryptophols (**1** → **2**) through the expediency of the 5-*O*-carbamate-directed metalaton group. Selective 4- and 6-substitution may be achieved via TMS protection and anionic *ortho*-Fries rearrangement tactics (**4**–**6**). Furthermore, organozinc and Grignard transition metal catalyzed cross coupling reactions may be adapted to derive powerful new protocols for C–C bond formation (**7a,b, 8**). The preliminary demonstration of tryptophol metalation chemistry (**12a,b**) also anticipates a broader perspective. The utility of this methodology, separate or combined, for the modification of indole derivatives in total synthesis endeavors or in pharmacological studies may be anticipated. Extension of these studies are in progress.

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Supplementary Material Available: General experimental and characterization data (27 pages).

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(15) 4-Hydroxy- and 4-aminoindoles are structural components of psylocibin and teleocidin alkaloids; see: Nakatsuka, S-i.; Masuda, T.; Asano, O.; Teramae, T.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 4327 and references cited therein.

(16) For the Li to Sn transmetalation method for s-electrophile introduction, see: Dickens, M. J.; Mowlem, T. J.; Widdowson, D. A.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 323.

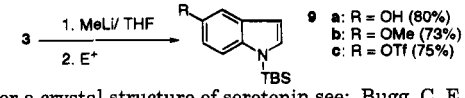
(17) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.

(18) Negishi, E.-i.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

(19) Use of modified Suzuki conditions ((1) $B(OMe)_3$; (2) $Pd(PPh_3)_4/2$ M K_2CO_3/DME/reflux) on **4**, E = Li, afforded the analogous cross-coupled product with loss of TBS in 19% yield. For other low yield couplings of pyridyl boron derivatives with 4-iodo- and 4-thallioindoles, see: Somei, M.; Amari, H.; Makita, Y. *Chem. Pharm. Bull. Jpn.* **1986**, *34*, 3971.

(20) Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680.

(21) In order to demonstrate deprotection of the 5-hydroxy function, the carbamate **3** was treated with MeLi and either worked up hydrolytically or treated with MeI or 2-pyN$(Tf)_2$ to give **9a**, **9b,** and **9c**, respectively. *Inter alia*, this may allow the preparation of 5-hydroxytryptamine analogues.



(22) For a crystal structure of serotonin see: Bugg, C. E.; Thewalt, U. *Acta Crystallogr. Sect. B* **1972**, *28*, 82.