ORGANIC LETTERS

2002
Vol. 4, No. 5
815−817

Rapid Route to 3,4-Substituted Indoles via a Directed Ortho Metalation–Retro-Mannich Sequence

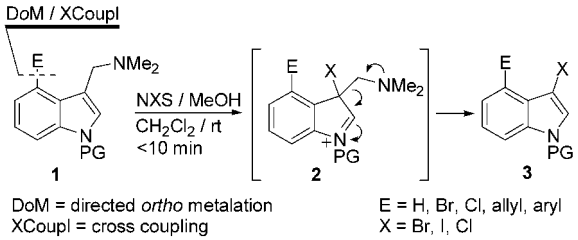
Brian Chauder, Andrew Larkin, and Victor Snieckus*

Department of Chemistry, Queen's University, Kingston, ON, K7L 3N6, Canada

snieckus@chem.queensu.ca

Received December 30, 2001

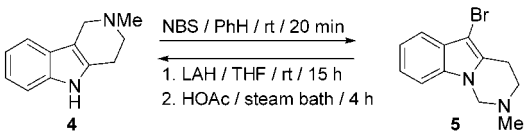
ABSTRACT



In the presence of NXS (X = Br, I, Cl), gramine derivatives 1, derived by combined directed ortho metalation (DoM)–cross-coupling sequences, rapidly undergo retro-Mannich fragmentation (2) to afford 3-halo indoles 3 in 37–88% yields. A conceptually new methodology to diverse 3,4-substituted indoles (10, 11, 13) is thereby introduced.

We report a new and unique route to 3,4-substituted indoles **3** based on a combined metalation and retro-Mannich sequence, **1**→ **3**. This route proceeds via a highly regioselective C-4 lithiation of gramine discovered by Iwao[1] and our finding,[2] of some vintage, concerning the interconversion of tetrahydro-γ-carboline **4** and tetrahydropyrimidoindole **5** ring systems that involves, in part, a Br^+-initiated retro-Mannich fragmentation (Scheme 1).

Scheme 1



Methods for de novo C-4-substituted indole ring construction (inter alia, Fischer, Madelung, and Reissert) suffer from regioisomer production or dependency on synthesis of specifically polyfunctionalized benzenes.[3] Among the few methods for direct C-4 substitution, the Iwao procedure[1] is exceptional in its brevity and scope. The DoM−retro-Mannich protocol delineated herein demonstrates rapid access to 3,4-differentially halogenated (Table 2, entries 1 and 2), 4-substituted 3-haloindoles (entries 4 and 5) and, via transition metal catalyzed coupling processes, interesting C−C bond construction motifs (Scheme 2 and Table 3). In view of the considerable effort needed to obtain valuable 4-substituted indoles,[4] the present methodology provides a short and general route with potential application for the preparation of less accessible bioactive indoles and tryptamines and new conceptual tools for viewing indole natural product synthetic targets.

(1) Iwao, M. *Heterocycles* **1993**, *36*, 29.
(2) Bhandari, K. S.; Snieckus, V. *Synthesis* **1971**, 327.

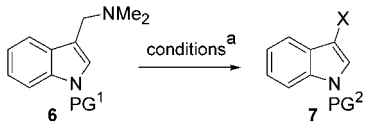
(3) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045 and refs cited therein. For Pd-catalyzed heteroannulation methods, see: Soederberg, B. C.; Schriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838 and a comprehensive list of refs therein.

(4) (a) Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267. (b) Hollins, R. A.; Colnago, L. A.; Salim, V. M.; Seidl, M. C. *J. Heterocycl. Chem.* **1979**, *16*, 993. (c) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797 and refs cited therein. (d) Somei, M.; Amari, H.; Makita, Y. *Chem. Pharm. Bull. Jpn.* **1986**, *34*, 3971 and refs cited therein. (e) Hegedus, L. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (f) Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983.

10.1021/ol017310m CCC: $22.00
Published on Web 02/05/2002

In the test experiment of the retro-Mannich fragmentation, *N*-TIPS gramine, when subjected to NBS, afforded, within minutes, the 3-bromo derivative in essentially quantitative yield (Table 1, entry 1). Similarly, the corresponding

Table 1. 3-Haloindoles **7** by Retro-Mannich Fragmentation of Gramine **6**

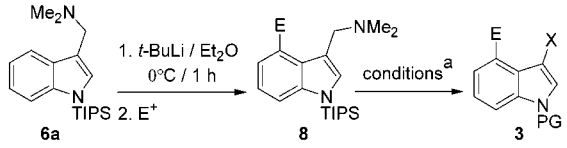


entry	**6**	PG^1	conditions[a]	**7**	X	PG^2	yield (%)[b]
1	**6a**	TIPS	a	**7a**	Br	TIPS	98
2	**6a**	TIPS	b	**7b**	Cl	TIPS	73
3	**6b**	H	c, d	**7c**	I	Boc	83−90
4	**6b**	H	c, e	**7d**	I	SO_2Ph	78
5	**6c**	Boc	f	**7e**	CHO	Boc	76

[a] (a) NBS/CH_2Cl_2/MeOH/rt/2 min; (b) NCS/CH_2Cl_2/MeOH/rt/15 min; (c) NIS/MeOH/0 °C/5 min; (d) $(Boc)_2O$/Et_3N/catalytic DMAP/CH_2Cl_2/rt/15 min; (e) $PhSO_2Cl$/NaOH/catalytic Bu_4NBr/PhMe/rt/30 min; (f) 2 equiv NBS/catalytic AIBN/py/CH_2Cl_2/reflux/10 min. [b] Isolated yields after chromatography or crystallization.

3-chloroindole was prepared via reaction with NCS (entry 2). Reaction of *N*-TIPS gramine with NIS, however, resulted only in decomposition products. This is not entirely surprising since 3-iodoindoles are reported to be unstable.[5]

Table 2. Synthesis of 3,4-Disubstituted Indoles **3** via DoM−Retro-Mannich Sequence

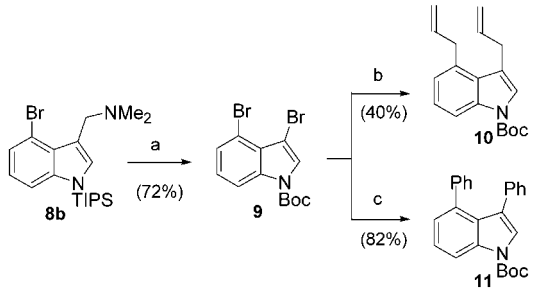


					3, yield (%)[b]	
entry	**8**	E^+	E	yield (%)[b]	**3a**, X = Br PG = TIPS	**3b**, X = I PG = Boc
1	**8a**	Cl_3C-CCl_3	Cl	64	80	37
2	**8b**	$BrCH_2CH_2Br$	Br	56	84	88
3	**8c**	$(TMSO)_2$	OH	66	decomp	decomp
4	**8d**	DMF	CHO	51	79	42
5	**8e**	TMSCl	TMS	62	83	63

[a] Bromination: NBS/CH_2Cl_2/MeOH/rt/2 min. Iodination: (1) TBAF THF/rt/10 min; (2) NIS/MeOH/0 °C/5 min; (3) $(Boc)_2O$/Et_3N/catalytic DMAP/CH_2Cl_2/rt/15 min. [b] Isolated yields after chromatography.

Nevertheless, treatment of *unprotected* gramine with NIS at 0 °C resulted in smooth conversion to 3-iodoindole, which, upon immediate N-protection, gave the *N*-Boc (entry 3) and *N*-SO_2Ph (entry 4) derivatives in high yields. This route uses inexpensive gramine as a starting material, requires no special precautions, tolerating moisture and oxygen, and compares favorably with established routes to 3-haloindoles.[6] In an unexpected but potentially useful observation, treatment of *N*-Boc gramine with NBS or NIS yielded the 3-formyl indole as the sole product, presumably via a radical mechanism (entry 5).[7] Reaction of **6a** with other electrophilic reagents, including TMSOTf, Tf_2O, selectfluor, ICl, Br_2, I_2, Ph-$(OCOCF_3)_2/I_2$, and $AlCl_3$/AcCl, gave either no reaction or a complex mixture of products.

Scheme 2[a]

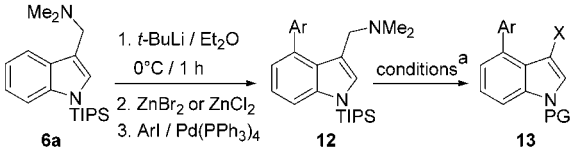


[a] Key: (a) (1) NBS/MeOH/CH_2Cl_2/rt/2 min; (2) TBAF/THF/rt/10 min; (3) $(Boc)_2O$/catalytic DMAP/Et_3N/CH_2Cl_2/rt/30 min. (b) $Bu_3SnCH_2CH{=}CH_2$/$Pd(PPh_3)_4$/PhMe/reflux/2 h. (c) $PhB(OH)_2$/DME/aqueous $Ba(OH)_2$/$Pd(PPh_3)_4$/reflux/15 min.

To connect the retro-Mannich process to the DoM reaction, a series of gramines **8** with C-4 carbon, silicon, oxygen, and halogen functional groups were prepared from **6a** as described by Iwao (Table 2).[1] These were subjected to bromination and iodination conditions to afford, with one exception (entry 3), 3,4-disubstituted indoles **3a** and **3b** in good overall yields.

For the development of new C-3 and C-4 C−C bond constructs, 4-bromogramine derivative **8b** was treated with

Table 3. Synthesis of 3,4-disubstituted Indoles **13** via Negishi − Retro-Mannich Sequence



				13, yield (%)[b]	
entry	**12**	Ar	yield (%)[b]	**13a**, X = Br PG = TIPS	**13b**, X = I PG = Boc
1	**12a**	*o*-tol	22	81	68
2	**12b**	Ph	53		24
3	**12c**	3-py	34	81	

[a] Bromination: NBS/CH_2Cl_2/MeOH/rt/2 min. Iodination: (1) TBAF/THF/rt/10 min; (2) NIS/MeOH/0 °C/5 min; (3) $(Boc)_2O$/Et_3N/catalytic DMAP/CH_2Cl_2/rt/15 min. [b] Isolated yields after chromatography.

(5) (a) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757. (b) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2690.

NBS followed by desilylation and *N*-Boc protection to give the 3,4-dibromo indole **9** in good overall yield (Scheme 2). Subjection of **9** to prototype Stille and Suzuki−Miyaura reactions led to the diallyl **10** and diphenyl **11**[8] derivatives, respectively, in modest yields.

The Negishi cross-coupling protocol may also be linked to the indole retro-Mannich reaction (Table 3). Thus, C-4 metalation of *N*-TIPS gramine **6a** with *t*-BuLi followed by treatment with anhydrous zinc bromide or zinc chloride and aryl halides under Pd-catalysis afforded 4-aryl derivatives **12** in low yields. Attempts to improve the yields by vigorously degassing the system were not successful. Nonetheless, treatment of **12** according to the retro-Mannich-bromination and -iodination protocols provided 3-halo-4-aryl indoles **13a** and **13b**, substrates for potential further cross-coupling chemistry.

In conclusion, a rapid entry into 3,4-difunctionalized indoles **3**, especially dihalogenated systems, via a DoM−retro-Mannich protocol has been established. Combination with cross-coupling regimens allows ready access to new indoles **10**, **11**, and **13a**,**b**. The overall methodology may suggest new strategies for bioactive molecule and alkaloid construction.

Acknowledgment. We are grateful to NSERC Canada for support under the Research Grant program. B.C. is a recipient of a Queen's Graduate Fellowship (QGF), 1999−2000.

Supporting Information Available: Experimental procedures for the metalation of **6a** and for the preparation of **3**, **7**, and **10**−**13** and characterization data for **7**, **8a**, **3a**,**b** (Table 2, entry 1), **10**, **11**, **12c**, and **13a** (Table 3, entry 3). This material is available free of charge via the Internet at http://pubs.acs.org.

OL017310M

(6) For 3-bromoindoles, see: Amat, M.; Sathyanarayana, S.; Hadida, S.; Bosch, J. *Heterocycles* **1996**, *43*, 1713 and refs cited therein. For 3-iodoindoles, see: Benhida, R.; Blanchard, P.; Fourrey, J.-L. *Tetrahedron Lett.* **1998**, *39*, 6849 and refs cited therein.

(7) For examples of debenzylation of amides using NBS/AIBN, see: Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 331.

(8) Structurally reminiscent of stereochemically interesting 1,8-substituted naphthalenes, see: Lunazzi, L.; Mazzanti, A.; Alvarez, A. M. *J. Org. Chem.* **2000**, *65*, 3200.