A Novel Tin-Mediated Indole Synthesis

Tohru Fukuyama,* Xiaoqi Chen, and Ge Peng

Department of Chemistry, Rice University
Houston, Texas 77251

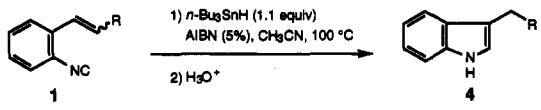
Received December 20, 1993

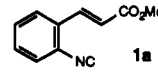
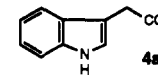
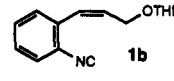
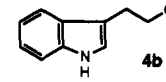
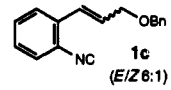
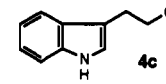
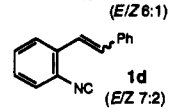
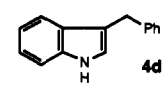
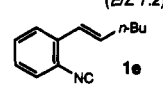
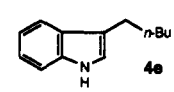
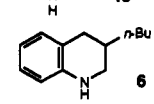
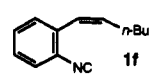
Indole is ubiquitous among a wide range of natural products. While a number of methods have already been well documented for the construction of this important nucleus, there appear to be few practical procedures available for the synthesis of 2,3-disubstituted indoles.[1] In this communication we report a versatile tin-mediated indole synthesis which is particularly suited for the preparation of 2,3-disubstituted indoles. Our method has a significant implication for the synthesis of a variety of indole alkaloids.

It has been known for quite some time that tin radicals add to isonitriles to form imidoyl radicals.[2] Despite the fact that some of the imidoyl radicals have been demonstrated to have strong synthetic potentials for inter- and intramolecular carbon–carbon bond formation,[3] simple α-stannoimidoyl radicals have attracted little attention among synthetic chemists. At the outset of this research, we reasoned that the α-stannoimidoyl radical **2**, generated from *o*-isocyanostyrene derivative **1** by addition of a tri-*n*-butyltin radical, should lead to the formation of the 2-stannylindole **3** through a radical cyclization and subsequent tautomerization as illustrated in Scheme 1.

Treatment of the isonitriles **1**[4] with tributyltin hydride and a catalytic amount of AIBN indeed gave the desired 3-substituted indoles **4** in high yields upon acidic workup (Table 1).[5] It should be noted that the substrates bearing radical-stabilizing substituents

Table 1. Synthesis of 3-Substituted Indoles



entry	substrate	product	isolated yield,%
1	 **1a**	 **4a**	91
2	 **1b**	 **4b**	83
3	 **1c** (*E*/*Z* 6:1)	 **4c**	68
4	 **1d** (*E*/*Z* 7:2)	 **4d**	83
5	 **1e**	 **4e**	51
		 **6**	33
6	 **1f**	**4e**	72
		6	18

Scheme 1

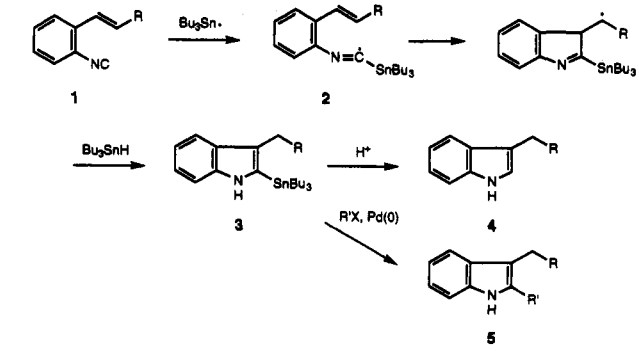
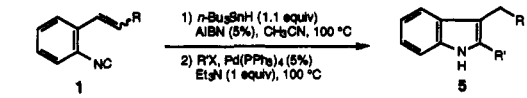
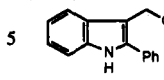
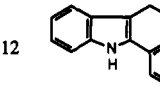
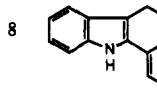
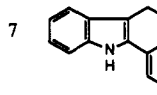
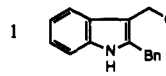
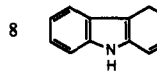
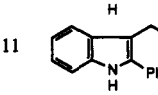
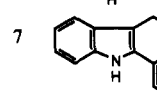
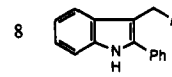


Table 2. One-Pot Synthesis of 2,3-Disubstituted Indoles



entry	substrate	R'X	equiv	time (h)	product	yield (%)
1	**1a**		1.2	5	 **5a**	82
2	**1a**		1.2	8	**5a**	68
3	**1a**		1.2	12	 **5b**	81
4	**1a**		1.2	3	**5b**	75[a]
5	**1a**		3.0	8	 **5c**	58
6	**1a**		3.0	7	 **5d**	64
7	**1a**		3.0	1	 **5e**	71[b]
8	**1a**		3.0	8	 **5f**	71[c]
9	**1b**		3.0	11	 **5g**	63
10	**1b**		3.0	7	 **5h**	49[a]
11	**1f**		3.0	8	 **5j**	65

[a] LiCl (5 equiv) and 10% volume of DMF were added. [b] No Et_3N was added. [c] CuI (1 equiv) was added.

at the β-position gave excellent yields (Table 1, entries 1 and 4). While a substantial amount (33%) of the tetrahydroquinoline **6**

(1) (a) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1. (b) Saxton, J. E. *Indoles*, Part Four; Wiley-Interscience: New York, 1983.
(2) Saegusa, T.; Kobayashi, S.; Ito, Y.; Yasuda, N. *J. Am. Chem. Soc.* **1968**, *90*, 4182.
(3) (a) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1320. (b) Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin. Trans. 1* **1986**, 1591. (c) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1989**, 757. (d) Bachi, M.; Denenmark, D. *J. Am. Chem. Soc.* **1989**, *111*, 1886. (e) Bachi, M.; Denenmark, D. *J. Org. Chem.* **1990**, *55*, 3442. (f) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127.

0002-7863/94/1516-3127$04.50/0

was formed from the *E*-substrate **1e** (entry 5), the problem could be alleviated by employing the *Z*-substrate **1f** (entry 6).

The important ramification of the above finding is that the hitherto unknown, N-unprotected 2-stannylindoles **3** have become readily available for further manipulation. To the best of our knowledge, the chemistry of 2-stannylindole has not been developed extensively, presumably because metalation of the N-protected indole has been the only practical method for synthesizing it.[6,7] Since 2-stannylindoles **3** were prone to undergo facile destannylation during workup, the Stille's palladium-mediated coupling[8] was performed on the crude reaction mixture immediately after the completion of the indole synthesis. As expected, the one-pot Stille coupling proceeded smoothly to give the desired 2,3-disubstituted indoles **5** in 49–82% yields as shown in Table 2. A few comments are worthy of note. As reported by Stille,[8c] addition of LiCl was essential for successful couplings with triflates (Table 2, entries 4, 6, and 10). When *trans*-1-iodohexene was used, addition of 1 equiv of CuI was needed to suppress the formation of the undesired 2-(1-butylethenyl)indole (entry 8).[9]

Since a wide variety of functional groups are known to tolerate both radical and palladium-mediated reactions, our efficient synthesis paves the way for a facile construction of a range of 3- or 2,3-substituted indoles from readily accessible isonitriles. Application of our method to the total synthesis of indole alkaloids is currently underway in our laboratories.

Acknowledgment. This research was supported by the National Institutes of Health (Grant CA28119) and the Robert A. Welch Foundation.

Supplementary Material Available: Details of experimental procedures and copies of ^{1}H NMR, ^{13}C NMR, IR, and MS spectral data of indole products (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(4) Methyl *o*-isocyanocinnamate (**1a**) was prepared from *o*-iodoaniline in a three-step sequence in 86% overall yield ((1) HCO_2H, Ac_2O, Py, CH_2Cl_2, 23 °C; (2) CH_2=$CHCO_2Me$, $Pd(OAc)_2$, (*o*-tol)$_3$P, Et_3N, CH_3CN, 80 °C; (3) $COCl_2$, Et_3N, CH_2Cl_2, 0 °C). Other isonitriles **1b–f** were similarly prepared in 61–82% overall yields from *o*-iodoformanilide by palladium-mediated coupling reactions.

(5) A typical experimental procedure is as follows. A solution of an isonitrile (0.85 mmol), *n*-Bu_3SnH (0.93 mmol), and AIBN (0.04 mmol) in 5 mL of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. The reaction mixture was partitioned between 3 N HCl and ether. After the ethereal layer was washed with a saturated KF solution, the desired indole was separated by flash silica gel chromatography.

(6) (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (b) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7.

(7) Palmisano, G.; Santagostino, M. *Helv. Chim. Acta* **1993**, *76*, 2356.

(8) (a) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (b) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(9) Liebeskind, L. S.; Feng, R. W. *J. Org. Chem.* **1990**, *55*, 5359.