Radical Cyclization of 2-Alkenylthioanilides: A Novel Synthesis of 2,3-Disubstituted Indoles

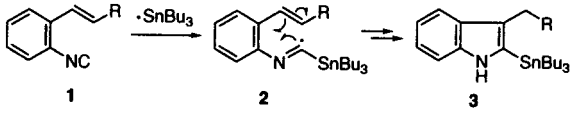
Hidetoshi Tokuyama, Tohru Yamashita, Matthew T. Reding, Yosuke Kaburagi, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences
The University of Tokyo
CREST, Japan Science and Technology Corporation (JST)
7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

Received October 22, 1998

The indole nucleus is present in a wide range of natural products, and the synthesis of this important structure has been a steady topic of interest for many years.[1] Among the numerous methods that have been developed for the synthesis of indoles, few practical and mild procedures are available for the construction of 2,3-disubstituted indoles.[2] Specifically, although the venerable Fischer indole synthesis still sees frequent use, the general necessity for acid and heat often produces significant purification difficulties.[3] Furthermore, the more recently developed Gassman and Fürstner indole syntheses require the frequently laborious synthesis of α-thiomethyl ketones and *o,N*-diacylanilines, respectively.[4,5] In this communication, we describe a novel indole synthesis that is carried out under mild radical cyclization conditions. In addition, we show that the thioanilide indole precursors may be easily synthesized in a modular fashion, to make accessible a wide range of 2,3-disubstituted indoles, in some cases with substituents on the carbocyclic aromatic ring as well.

In an earlier study, we reported that the α-stannoimidoyl radical **2**, generated by addition of tri-*n*-butyltin radical to 2-alkenylphenylisonitrile **1**, leads to the formation of 2-stannylindole **3** through radical cyclization and subsequent tautomerization (eq 1).[6] This methodology proved to be applicable to the synthesis

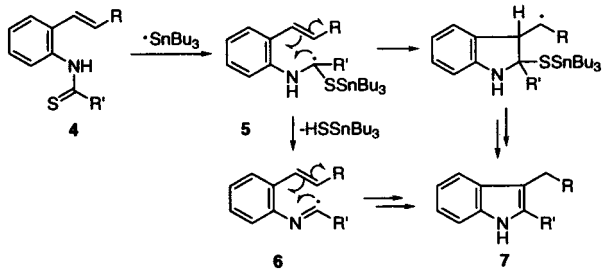


(1)

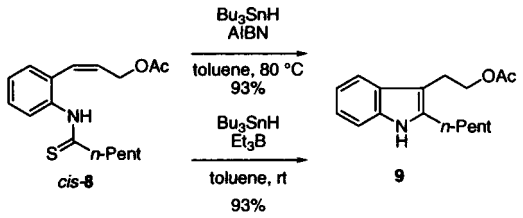
of a variety of 2-substituted and 2,3-disubstituted indoles. It has recently been reported that tin radicals add to thionoesters or thioamides to generate stabilized radical species.[7] With this in mind, we reasoned that tin radicals might add to thioamide derivatives such as 2-alkenylthioanilide **4** to form sp^3 (**5**) or imidoyl radical species (**6**), which might then undergo radical cyclization to furnish 2,3-disubstiuted indoles **7** (Scheme 1).

The 2-alkenylthioanilides *cis*- and *trans*-**8** were prepared from 2-iodoaniline in several steps (vide infra) and subjected to typical radical cyclization conditions. Gratifyingly, treatment of *cis*-**8** with tri-*n*-butyltin hydride and AIBN in toluene at 80 °C for 5 min resulted in the clean formation of the expected 2-*n*-pentyl-3-(acetoxyethyl)indole (**9**) in 93% isolated yield (Scheme 2).

Scheme 1



Scheme 2



Furthermore, a similar reaction was complete within 5 min at room temperature using Et_3B as the radical initiator,[8] to afford **9** in 93% yield.[9,10] The rate of the Et_3B-initiated reaction proved to be dependent upon the geometry of the olefin. For example, cyclization of *trans*-**8** afforded only 39% of **9** along with the recovered starting material (19%), even after stirring for 90 min at room temperature.[11]

As shown in Table 1, a wide range of both base- and acid-sensitive functional groups such as esters, THP ethers, and β-lactams could be introduced at the indole 2- and 3-positions.[12] In the case of a thioanilide derived from a chiral α-amino acid, no detectable racemization was observed after the indole formation.[13] In addition, we have found that hypophosphorous acid can be employed as an alternative radical reducing agent to tin hydride.[14] For example, 2-cyclohexylindole was prepared in 71% yield after heating a mixture of the substrate, hypophosphorous acid (10 equiv), triethylamine (15 equiv), and AIBN (1.1 equiv) in *n*-PrOH at 100 °C for 20 min.

The present protocol is also well-suited for the preparation of 2,3-disubstituted indoles bearing substituents on the carbocyclic aromatic ring. 5- or 6-Methoxyindoles could be synthesized by our method in about 80% yield (Table 2). Remarkably, a bromo-substituted carbocyclic ring survived the radical reaction with only a small amount of radical hydrodebromination to afford the corresponding 5-bromoindole.

(1) (a) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988,** *25*, 1. (b) Saxton, J. E. *Indoles*; Wiley-Interscience: New York, 1983; Part 4.

(2) Sundberg, R. J. *Indoles*; Academic Press: London, 1996 and references therein.

(3) Reference 2, Chapter 7.

(4) (a) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495. (b) Gassman, P. G.; Gilbert, D. P.; van Bergen, T. L. *J. Chem. Soc., Chem. Commun.* **1974**, 201.

(5) (a) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991. (b) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.

(6) (a) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (b) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043.

(7) (a) Bachi, M. D.; Bosch, E.; Denenmark, D.; Girsh, D. *J. Org. Chem.* **1992**, *57*, 6803. (b) Feldman, K. S.; Schildknegt, K. *J. Org. Chem.* **1994**, *59*, 1129.

(8) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1989**, *45*, 923.

(9) While comparable results were obtained using benzene, acetonitrile, or THF as solvents, the reaction was sluggish in ethanol and *tert*-butyl alcohol.

(10) A typical experimental procedure is as follows. To a stirred solution of 2-alkenylthioanilide (0.025 M in toluene) and *n*-Bu_3SnH (2.0 equiv) was added Et_3B (0.10 equiv, 1.0 M in hexane) at room temperature under an argon atmosphere. After TLC analysis showed that the starting material had been consumed, the reaction mixture was diluted with AcOEt, washed with saturated aqueous KF and brine, and dried over $MgSO_4$. Filtration and concentration on a rotary evaporator afforded the crude product. The desired indole was purified by flash column chromatography on silica gel.

(11) Under thermal conditions with AIBN as the radical initiator, however, *cis* and *trans* substrates afforded the corresponding indoles in comparable yields. For example, the reaction of *trans*-**8** was complete in 45 min at 80 °C to afford **9** in 75% yield.

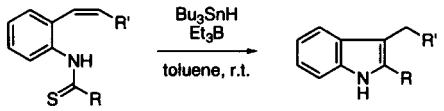
(12) The corresponding phenylthioamide and phenylethynylthioamide did not afford the desired indoles under the reaction conditions. Thioformamides afforded the corresponding formamide.

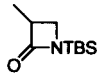
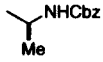
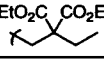
(13) A reduction of enantiomeric excess occurred during the conversion of the corresponding amide to the starting thioanilide (Lawesson's reagent (2 equiv) and pyridine (5 equiv) in toluene at 100 °C). Addition of pyridine was required to prevent further epimerization.

(14) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838.

10.1021/ja983681v CCC: $18.00
Published on Web 04/02/1999

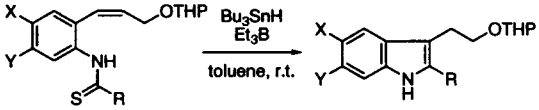
Table 1. Formation of 2,3-Disubstituted Indoles



R	R'	Bu_3SnH (eq)	Et_3B (eq)	time (min)	% yield[a]
Me	CH_2OAc	1.2	0.1	5	89
n-C_4H_9	CH_2OTHP	1.2	0.1	5	83
n-C_5H_{11}	CH_2OAc	1.5	0.1	5	93
c-Hex	CH_2OTHP	2.0	0.1	30	84
c-Hex	CH_2OH	*b*	*b*	20	71
1-adamantyl	CH_2OAc	10	0.1	15	36
Bn	CH_2OTHP	5.0	0.4	45	66
CH_2CO_2Et	CH_2OTHP	1.2	0.1	5	94
CH_2OCH_3	CH_2OAc	1.2	0.1	5	78
	CH_2OTHP	1.2	0.1	5	93
	CH_2OAc	3.0	0.1	5	82[c]
n-C_5H_{11}	*n*-C_4H_9	2.0	0.15	5	80
Me	CH_2CH_2OTBS	2.0	0.15	15	75
Me		2.0	0.15	15	68

[a] All yields are for isolated products. [b] AIBN (1.1 equiv) and H_3PO_2 (10 equiv) were used as a radical source and a radical reducing agent, respectively, in the presence of Et_3N (15 equiv). [c] Enantiomeric excess of the substrate and the product were 93% ee.

Table 2. Syntheses of 5- and 6-Substituted Indoles

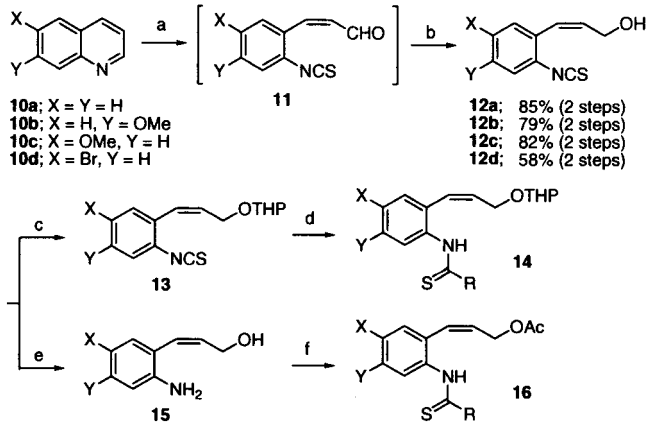


X	Y	R	Bu_3SnH (eq)	Et_3B (eq)	time (min)	% yield[a]
OMe	H	*n*-C_4H_9	2.0	0.1	5	79
OMe	H	CH_2CO_2Et	2.0	0.1	5	82
H	OMe	*n*-C_4H_9	2.0	0.25	15	82
Br	H	*n*-C_4H_9	2.0	0.1	5	81[b]

[a] All yields are for isolated products. [b] Ca. 3% of the corresponding debrominated product was isolated.

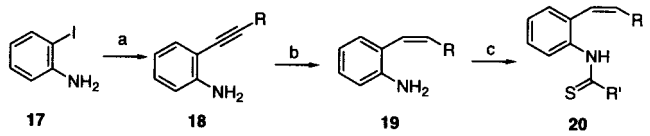
The requisite *cis*-2-alkenylthioanilides can be synthesized by one of three general methods developed in the course of this investigation. Method A begins with the treatment of quinolines **10a**−**d** with thiophosgene and barium carbonate to obtain *cis*-enals **11a**−**d**,[15] followed by immediate reduction with $NaBH_4$ to give the corresponding *cis*-cinnamyl alcohols **12a**−**d** in good yields over two steps (Scheme 3).[16] The conversion of the isothiocyanates into thioamides was carried out by THP protection of the hydroxyl group, followed by treatment of the resultant ethers **13** with Grignard reagents or lithium enolates.[17] Method B involves the hydrolysis of isothiocyanate **12a** to give aniline derivative **15**, which, after acylation, protection of the primary alcohol, and treatment with Lawesson's reagent, led to the desired thioamides **16** (Scheme 3).[17] Method C involves the palladium-catalyzed Sonogashira coupling of 2-iodoaniline (**17**) with terminal alkynes to afford 2-alkynylanilines **18**, which are then stereospecifically reduced with activated zinc to give exclusively *cis*-**19** (Scheme 4). Acylation followed by thionation with Lawesson's reagent furnished the desired 2-alkenylthioanilides **20**.[17]

Scheme 3. Methods A and B[a]



[a] (a)$CSCl_2$ (1.0 equiv), $BaCO_3$ (1.5 equiv), CH_2Cl_2/H_2O. (b) $NaBH_4$, CH_2Cl_2/MeOH. (c) DHP, CSA, CH_2Cl_2, 90%. (d) RMgX or Li enolate. (e) 5 M KOH, *t*-BuOH/H_2O, reflux, 80%. (f) RCOCl, $PhNEt_2$; Ac_2O, pyridine; Lawesson's reagent, toluene, 110 °C.

Scheme 4. Method C[a]



[a] (a) HC≡CR, $PdCl_2(PPh_3)_2$, CuI, Et_2NH. (b) Activated Zn, $BrCH_2$-CH_2Br, (CuBr, LiBr), EtOH. (c) 1. $CSCl_2$, $CaCO_3$. 2. RMgBr or 1. RCOCl, pyridine. 2. Lawesson's reagent, toluene, 110 °C.

Methods A and B give rise to 2-(3-oxypropenyl)thioanilides, which are then transformed into 2-indolylethanols by radical cyclization. The ease of conversion of the hydroxyl function to amines makes these compounds excellent precursors to the wide range of tryptamine-containing indole alkaloids. Methods A−C, together with the new indole formation protocol presented herein, represent a modular set of protocols for the construction of 2,3-disubstituted indoles and their carbocyclic ring congeners, with the 2-substituent arising from a carboxylic acid, Grignard reagent, or enolate, the 3-substituent from an alkyne or a 3-oxypropenyl fragment from a ring-opened quinoline, and the carbocyclic ring from quinolines or 2-iodoaniline.

In summary, we have demonstrated the facile and mild formation of 2,3-disubstituted indoles by radical cyclization of 2-alkenylthioanilides. This process is complementary to our previously reported protocol in which introduction of sp^3-hybridized substituents to the 2-position was difficult. The modular preparation of indole precursors, mild cyclization conditions, and compatibility with various substituents at the 2- and 3- positions as well as on the carbocyclic aromatic ring make this protocol a powerful addition to existing indole synthesis methodologies.

Acknowledgment. We thank Dr. S. I. Parekh of Abbott Laboratories for a valuable suggestion. This work was supported in part by the Ministry of Education, Sports and Culture, Japan. M.T.R. gratefully acknowledges the support of a Japan Science and Technology Corp. fellowship.

Supporting Information Available: Experimental details and analytical data for the isothiocyanates, thioanilides, and indole products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA983681V

(15) (a) Hull, R. *J. Chem. Soc. C* **1968**, 1777. (b) Hull, R.; van den Broek, P. J.; Swain, M. L. *J. Chem. Soc., Perkin Trans. 1* **1975**, 922.

(16) Quinolines **10c**,**d** are commercially available. Quinoline **10b** as well as **10c**,**d** are easily prepared by the Skraup synthesis, see: Manske, R. H. F.; Kulka, M. *Org. React.* **1953**, *7*, 59.

(17) See the Supporting Information for detailed experimental procedures.