Synthesis of 2,3-Dialkylindoles from 2-Alkenylphenylisocyanides and Imines by Silyltelluride- and Tin Hydride-Mediated Sequential Radical Reactions

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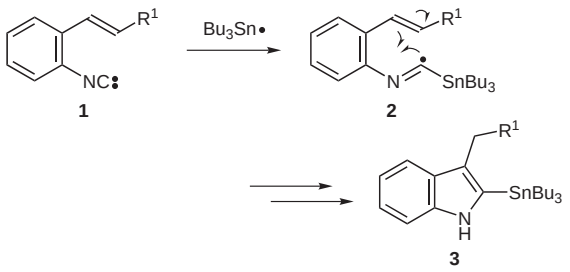
Abstract: A new method for the synthesis of 2,3-dialkylindoles is described. The silyltelluride-mediated coupling reaction of imines and 2-alkenylphenylisocyanides selectively occurred at the isocyanide moiety to give the corresponding imidoyltelluride. Tin hydride-mediated intramolecular cyclization of the imidoyltelluride affords 2,3-dialkylindoles in good to excellent combined yields.

Key words: indoles, radical reactions, cyclization, isocyanides, tellurium

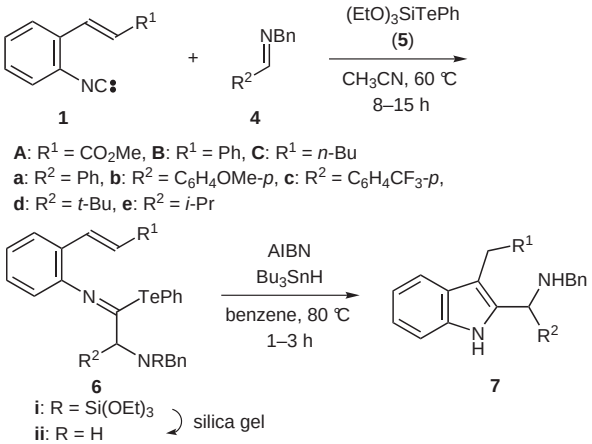
The invention of new synthetic routes to indoles has attracted a great deal of attention due to their significant biological activities.[1] While a number of methods have already been reported to construct indole skeleton under acid-, base-, and transition metal-catalyzed conditions,[2] radical-mediated synthesis, which shows high functional group compatibility with chemo- and regioselectivity, would be advantageous in view of the rich functionalities present in many naturally occurring indole derivatives. In this respect, one of us has already reported the synthesis of 2-stannylindole **3** by tributyltin radical promoted intramolecular cyclization of 2-alkenylphenylisocyanide **1** through imidoyl radical **2** (Scheme 1).[3,4] Furthermore, the alkenylstannane functionality in **3** could be further transformed to carbon substituents by the Migita–Stille coupling reactions.[3c] Therefore, this method represents a rare example which can be practically applicable to the synthesis of highly functionalized 2,3-disubstituted indoles.[5]



Scheme 1

This method, however, still have drawbacks; the synthesis of carbon-substituted derivatives requires the intermediacy of unstable 2-stannylindoles, and the C-2 carbon substituent is limited to alkenyl, aryl, and alkynyl groups. While the use of alkyl radicals instead of the tin radical seems to be an obvious alternative, the most standard method for the generation of alkyl radicals from alkyl halides and tin radical could not be applicable. This is probably because tin radical would possess similar reactivities towards isocyanides and alkyl halides, and, thus, selective alkyl radical generation would be difficult, as an analogy of the reactivity of silyl radicals.[6]

One of us has recently reported that organotellurium compounds thermally react with isocyanides to give imidoyltellurides without the use of tin radicals.[7] Since the reaction of imines with triethoxysilylphenyltelluride (**5**) produces the corresponding α-aminomethyltellurides (e.g., compound **9**), and, subsequently, the corresponding α-aminomethyl radicals under mild thermal conditions,[8] we chose this method for the radical generation and investigated the reaction with isocyanide **1**. We report here a new protocol to construct 2,3-dialkylindoles based on the new synthetic strategy.[9] While a few examples have been reported on the intramolecular cyclization of alkyl-substituted imidoyl radical to give the 2,3-dialkylindole,[10,11] their synthetic scope is rather limited due to the difficulty to synthesize the radical precursors.



Scheme 2

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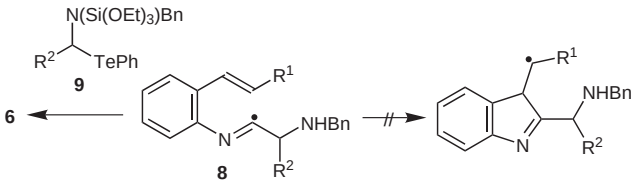
The coupling reaction was carried out by heating a solution of **1A** ($R^1 = CO_2Me$), imine **4a** (R^2 = Ph, 2.0 equiv), and **5** (2.0 equiv) in acetonitrile at 60 °C for 10 hours (Scheme 2). We surprisingly found that the reaction exclusively afforded imidoyltelluride **6Aa–i** [$R^1 = CO_2Me$, R^2 = Ph, R = $Si(OEt)_3$], which was hydrolyzed during silica gel chromatography to give **6Aa–ii** ($R^1 = CO_2Me$, R^2 = Ph, R = H) in 96% isolated yield (Table 1, entry 1). We could not observe the formation of cyclized product at all. Several attempts to obtain cyclized product directly from **1A** and **4a** in a selective manner were unsuccessful so far by changing solvents, reaction temperatures, and concentration of the substrates. For example, the reaction at 100 °C afforded **6Aa** and cyclized product **7Aa** in 20% and 12% yields, respectively, together with oligomers of **1A** as judged by gel permeation chromatography analyses.[12]

It has been reported that the first-order rate constants of intramolecular cyclization of acyl radicals, which possess isoelectronic structure with imidoyl radicals, are 10^3–10^5 s^{-1}.[13] On the other hand, the phenyltellanyl group transfer with alkyl radicals is reported to proceed at the second-order rate constant of 10^7 M^{-1} s^{-1}.[14] Therefore, the failure of intramolecular cyclization of the imidoyl radical **8** can be primarily attributed to the faster phenyltellanyl group transfer with **9** to give **6** rather than the intramolecular cyclization (Scheme 3).[15] In contrast to organotellurium intermediate **9** which possesses thermally labile sp^3-carbon–tellurium bond, the sp^2-carbon–tellurium bond in imidoyltelluride **6** is thermally stable. Therefore, once imidoyltelluride **6** forms, regeneration of imidoyl radical **8** from **6** does not occur under the reaction conditions.



Scheme 3

The imidoyltelluride could be reactivated upon the reaction with tin radical, and subsequent cyclization of imidoyl radical **8** afforded the cyclized product. Thus, **6Aa** was converted to indole **7Aa** in 87% yield by treatment with tributyltin hydride (1.2 equiv) in the presence of AIBN (0.2 equiv) in benzene at 80 °C for one hour.[7e,8]

The stepwise synthesis of indole **7** from **1** and **4** was generally applicable to a variety of substituents R^1 and R^2 of **1** and **4**, respectively, as summarized in Table 1.[16] For the imine part, both aromatic and aliphatic imines (**4a–e**) were coupled with **1A** to give **6ii** after hydrolysis of silicon–nitrogen bond (entries 1–5). The coupling efficiencies were slightly affected by the electron-withdrawing group on the phenyl group (entries 1 and 2 vs. 3) and the steric bulkiness of the alkyl substituents (entry 4 vs. 5), but the desired imidoyltellurides were formed in good to excellent yields in all cases. The R^1 group of **1** did not affect the coupling efficiency of the first step, and the desired products were formed in good to excellent yields (entries 6–9). The second step, namely the intramolecular cyclization also proceeded in good to excellent yields in all cases irrespective of the R^1 and R^2 substituents of **6ii**.

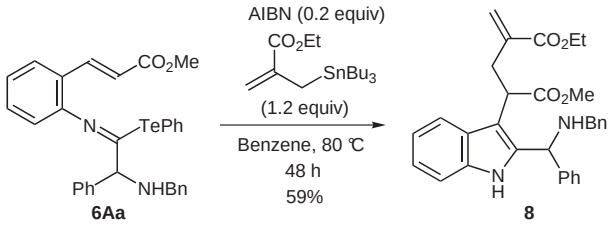
Table 1 Synthesis of 2,3-Disubstituted Indoles

Entry	**1**	**4**	Yield (%)[a]	
	R^1	R^2	**6ii**	**7**
1	CO_2Me (**A**)	Ph (**a**)	96	87
2	CO_2Me (**A**)	4-$CH_3OC_6H_4$ (**b**)	96	88
3	CO_2Me (**A**)	4-$CF_3C_6H_4$ (**c**)	68	70
4[b]	CO_2Me (**A**)	*t*-Bu (**d**)	80	81
5[b]	CO_2Me (**A**)	*i*-Pr (**e**)	65	78
6	Ph (**B**)	4-$CH_3OC_6H_4$ (**b**)	95	80
7[b]	Ph (**B**)	*t*-Bu (**d**)	79	66
8	*n*-Bu (**C**)	4-$CH_3OC_6H_4$ (**b**)	83	78
9[b]	*n*-Bu (**C**)	*t*-Bu (**d**)	82	81

[a] Isolated yield after purification by silica gel column chromatography.
[b] Since the hydrolysis of silicon–nitrogen bond of **6i** did not complete during the column chromatography, the reaction mixture was stirred with silica gel in CH_2Cl_2 for 1 h at r.t. before purification.

We next examined one-pot synthesis, but it turned out to be unsuccessful. For example, the reaction mixture containing **6Aa–i** prepared from **1A** and **4a** in the same manner was treated with tributyltin hydride (1.2–2.0 equiv) in the presence of AIBN at 80 °C, but we isolated indole **7Aa** in only 22% yield from complex reaction mixtures. Control experiments suggested that the low cyclization efficiency was attributed to the existence of triethoxysilyl group in **6i**. Thus, while the tributyltin hydride-mediated cyclizations of **6Ad–ii** ($R^1 = CO_2Me$, R^2 = *t*-Bu, R = H) afforded cyclized **7Ad** in 81% yield (Table 1, entry 4), that of isolated **6Ad–i** [$R^1 = CO_2Me$, R^2 = *t*-Bu, R = $Si(OEt)_3$] resulted in 42% yield of **7Ad** after hydrolysis of silicon–nitrogen bond. This is probably because bulky triethoxysilyl group hindered to take suitable conformation(s) for the cyclization in the imidoyl radical intermediate.

The virtue of the current method is the ease of further incorporation of substituents to form more structurally elaborated indoles. For example, treatment of **6Aa–ii** with ethyl 2-(tributylstannylmethyl)acrylate (1.2 equiv) in the presence of AIBN (0.2 equiv) resulted in the formation of allylated product **8** in 59% yield (Scheme 4).



Scheme 4

In summary, we have developed the new synthetic route to 2,3-dialkylindoles from 2-alkenylphenylisocyanide and imines by silyltelluride- and tin hydride-mediated sequential radical reactions. This method would be useful for the combinatorial synthesis of indoles by modular approach, because the reaction is insensitive to the R^1 and R^2 groups in **1** and **4** as well as the reagents used for the cyclization reaction. In addition, the both reactions proceed under mild thermal conditions to give desired products in high combined yields. Therefore, this method would find various synthetic applications especially for the synthesis of highly functionalized indoles.

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(16) **Typical Experimental Procedures.**
To a solution of isocyanide **1A** (188 mg, 1.0 mmol) and imine **4a** (389 mg, 2.0 mmol) in MeCN (1 mL) was added silyltelluride **5** (739 mg, 2.0 mmol) under nitrogen atmosphere, and the resulting solution was stirred at 60 °C for 10 h. Solvent was removed under reduced pressure followed by purification by silica gel column chromatography to give imidoyltelluride **6Aa**–**ii** in 96% yield (562 mg, 0.96 mmol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.68 (br s, 1 H), 3.77 (s, 3 H), 3.96 (d, *J* = 13.2 Hz, 1 H), 4.06 (d, *J* = 13.2 Hz, 1 H), 4.59 (s, 1 H), 6.33 (d, *J* = 16.1 Hz, 1 H), 6.82 (d, *J* = 7.8 Hz, 2 H), 6.95 (t, *J* = 7.5 Hz, 2 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 7.17–7.20 (m, 3 H), 7.27–7.31 (m, 4 H), 7.34–7.37 (m, 4 H), 7.43 (t, *J* = 7.3 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 16.0 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 51.61, 52.15, 70.15, 112.84, 118.58, 118.76,

124.42, 125.29, 127.11, 127.71 (two peaks), 128.01, 128.38 (two peaks), 128.47, 128.59, 129.05, 130.82, 138.84, 139.72, 140.70, 141.37, 151.46, 167.26. HRMS (FAB): *m/z* calcd for $C_{31}H_{29}O_2N_2{}^{130}Te$ $(M)^+$: 591.1247; found: 591.1294. A solution of imidoyltelluride **6Aa**–**ii** (59 mg, 0.10 mmol) and AIBN (3.3 mg, 0.02 mmol) tributyltin hydride (32 mg, 0.12 mmol) in benzene (2 mL) was heated to 80 °C with stirring under nitrogen atmosphere for 1 h. Solvent was removed under reduced pressure followed by purification by silica gel column chromatography and GPC to give indole **7Aa** in 87% yield (23 mg, 0.060 mmol). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.72 (br s, 1 H), 3.55 (s, 3 H), 3.68 (s, 2 H), 3.79 (s, 2 H), 5.22 (s, 1 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 7.15 (t, *J* = 7.5 Hz, 1 H), 7.24–7.35 (m, 9 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 7.56 (d, *J* = 7.9 Hz, 1 H), 8.58 (br s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.09, 51.78, 52.01, 58.21, 105.06, 110.95, 118.55, 119.63, 121.91, 127.22, 127.30, 127.67, 128.17, 128.53, 128.57, 128.78, 134.93, 136.89, 139.75, 141.52, 172.13. HRMS (FAB): *m/z* calcd for $C_{25}H_{24}O_2N_2$ $[M]^+$: 384.1838; found: 384.1832.