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1,6-Stannatropic Strategy: Effective Generation and Cyclization of 1,5-Dipoles from *o*-Stannylmethylated Thioanilides or Phenyl Isothiocyanates

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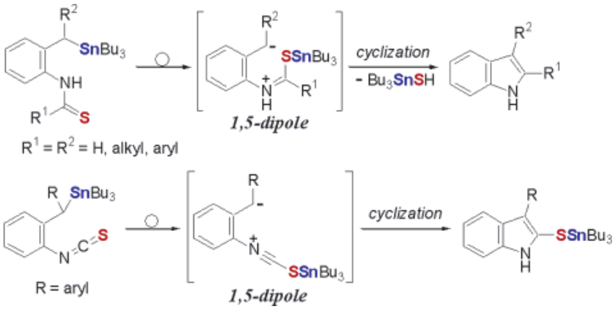
ABSTRACT

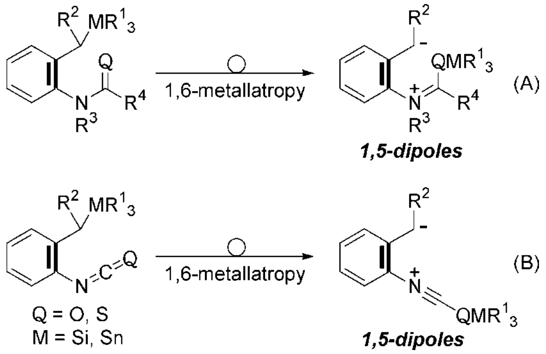


A new method for the generation of 1,5-dipoles from *o*-stannylmethylated thioanilides via 1,6-stannatropy under neutral conditions was developed. Cyclization of the 1,5-dipoles afforded indole derivatives effectively. The strategy has potential for application to the generation of alternative 1,5-dipoles from *o*-stannylmethylated aryl isothiocyanates leading to indole derivatives having a stannylthio group that was readily converted to other functional groups.

Cyclization[1] and cycloaddition[2] of 1,5-dipoles, which are 1,3-dipoles directly bound to an unsaturated moiety, are prominent methods for construction of heterocyclic rings. While only a few examples of [5+2] cycloadditions of 1,5-dipoles leading to seven-membered heterocycles are known, cyclization of 1,5-dipoles via 1,5-electrocyclic ring closure for the synthesis of five-membered heterocycles was studied actively. 2-Vinylpyridinium ylides, which are representative vinyl-substituted azomethine ylides, serve as useful precursors of indolizine derivatives via 1,5-dipolar cyclization.[3] On the other hand, we have created a potential strategy for the generation of azomethine ylides from *N*-silyl- or *N*-stannylmethylated amide derivatives via thermal 1,4-sila/stannatropy.[4]

If a vinyl group, here a benzene ring, is introduced between a silyl or stannyl group substituted carbon and amide nitrogen, the reactive molecule would induce 1,6-metallatropy leading to a 1,5-dipole, which is a kind of vinylogous azomethine ylide (Scheme 1A). The dipoles would furnish

Scheme 1



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indole derivatives through 1,5-dipolar cyclization or 6π electrocyclization.

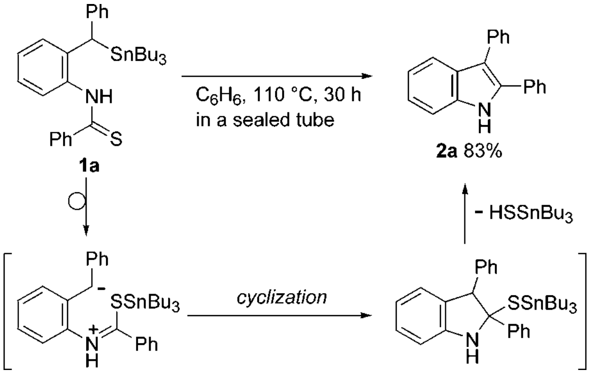
Moreover, our strategy can be expanded to the generation of 1,5-dipoles from *o*-metallomethylated phenyl isothiocyanates (Scheme 1B).

Herein we report on the generation of 1,5-dipoles from *o*-metallomethylated anilide and isothiocyanate derivatives via 1,6-metallatropy and cyclization of the 1,5-dipoles leading to indole derivatives. Various biologically active compounds having indole rings are found in nature, and the indole derivatives are important key compounds for the synthesis of a variety of natural products, pharmacologically interesting compounds,[5] and various functional materials.[5a]

Our first investigation was to observe the behavior of *o*-metallomethylated anilides under thermal conditions. When benzene solutions of *o*-silylmethylated anilides or *o*-silylmethylated thioanilides were heated in sealed tubes, the reactions did not proceed at all even at 200 °C. Our preliminary experiments clarified the tendency toward the migration of the metallo groups as Sn > Si, where a larger affinity between tin and sulfur was observed. These facts encouraged us to study the thermal reaction of *o*-stannylmethylated thioanilides. Thus, we successfully found that heating a benzene solution of thioanilide **1a** at 110 °C for 30 h gave 2,3-diphenylindole **2a** in high yield (Scheme 2).

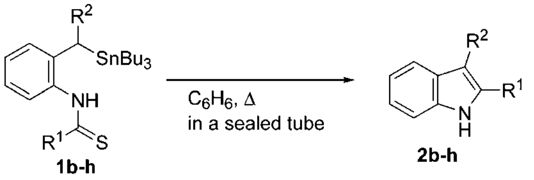
Indole **2a** might be formed via (1) the generation of a 1,5-dipolar intermediate from thioanilide **1a** by thermal 1,6-migration of the tin atom (1,6-stannatropy), (2) electrocyclization of the 1,5-dipole, and (3) elimination of tributylstannanethiol causing aromatization.[6]

Scheme 2



With an acceptable result for the formation of an indole from *o*-stannylmethylated thioanilide **1a** in hand, the versatile method was extended to the synthesis of a variety of thioanilides **1b−h** (Table 1).

Table 1. Synthesis of Indole Derivatives from *o*-Stannylmethylated Thioanilides via 1,6-Stannatropy



entry	substr.	R^1	R^2	temp (°C)	time (h)	product	yield (%)
1	**1b**	4-MeOC$_6$H$_4$	Ph	110	45	**2b**	84
2	**1c**	4-CF$_3$C$_6$H$_4$	Ph	110	15	**2c**	70
3	**1d**	styryl	Ph	110	5	**2d**	48
4	**1e**	Ph	4-ClC$_6$H$_4$	110	12	**2e**	82
5	**1f**	H	Ph	200	9	**2f**	50
6	**1g**	Me	Ph	200	12	**2g**	55
7	**1h**	Ph	H	200	96	**2h**	58

The reaction of thioanilide **1b**, having an electron-donating group on the thiocarbonyl aromatic ring, afforded indole derivative **2b** in high yield (entry 1). In contrast, the introduction of an electron-withdrawing group at the same position accelerated the reaction extensively (entry 2). In the case of thioanilide **1d**, having a styryl group, the reaction also proceeded smoothly to give the corresponding indole **2d** (entry 3). A chloro-substituted phenyl group as R^2 might have contributed to the stabilization of the dipolar intermediate, leading to indole **2e** (entry 4). As shown in entries 5−7, the generation of less-stabilized 1,5-dipoles from **1f−h** (R^1 = H, Me or R^2 = H) could be realized to cyclize to the

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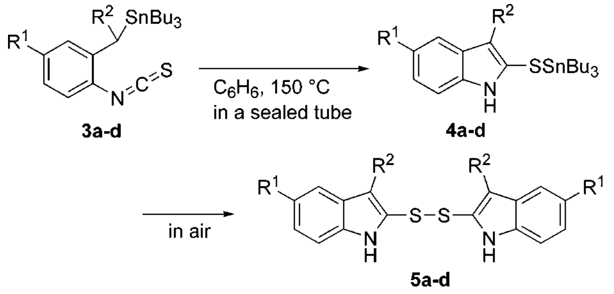
(6) Because initial reaction rates of the reactions at different initial concentrations are the same, the migration of the stannyl group of thioanilides **1** should occur intramolecularly. See Supporting Information data.

corresponding indoles, respectively, although a higher reaction temperature was required. Therefore, the present 1,6-stannatropic strategy was found to be highly effective for the synthesis of substituted indole derivatives.

The 1,6-stannatropic protocol for the generation of 1,5-dipoles from *o*-stannylmethylated thioanilides was expected to be applicable to an alternative sulfur-containing conjugated system. If a molecule having an isothiocyanate moiety such as **3a** is employed, a 1,6-shift of the stannyl group onto sulfur atom might generate the corresponding 1,5-dipole, including a carbon−nitrogen triple bond (Scheme 1B). When a benzene solution of *o*-stannylmethylated phenyl isothiocyanate **3a** was heated in a sealed tube at 150 °C for 15 h, the expected reaction occurred to give tributyltin 2-indolyl sulfide **4a** in an excellent yield (Table 2, entry 1). Because some examples of biologically active indole derivatives bearing sulfur functional groups at the 2-position have been reported,[7] the method would be useful for the synthesis of such compounds.

Table 2. Synthesis of Disulfides **5** from *o*-Stannylmethylated Isothiocyanates **3** via 1,6-Stannatropy



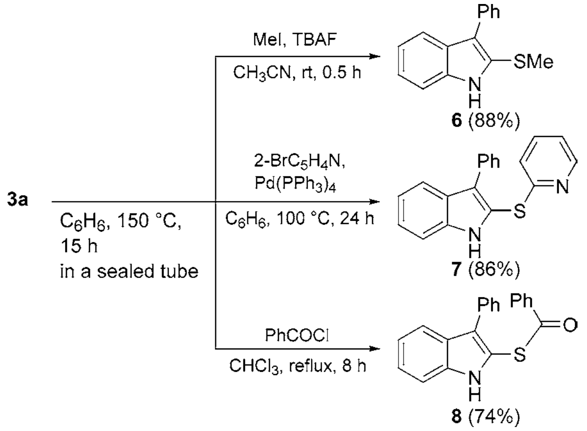
entry	substrate	R^1	R^2	time (h)	product	yield (%)
1	**3a**	H	Ph	15	**5a**	88 (91)[a]
2	**3b**	Cl	Ph	96	**5b**	96
3	**3c**	OMe	Ph	60	**5c**	94
4	**3d**	H	4-ClC$_6$H$_4$	72	**5d**	85

[a] Isolated yield of **4a** under dry nitrogen atmosphere.

The cyclization of *o*-stannylmethylated phenyl isothiocyanates **3a**−**d** is listed in Table 2. In these cases, disulfides **5a**−**d** were obtained after purification by silica gel column chromatography because of high susceptibility of 2-indolyl sulfides **4** toward hydrolysis and spontaneous oxidation. When isothiocyanates **3b**,**c** having electron-withdrawing or -donating, chloro, or methoxy group, at the position of R^1 were employed, the reactions afforded disulfides **5b**,**c** in excellent yields, albeit with a longer reaction time than that for **3a** (entries 2 and 3). The reaction of isothiocyanate **3d**, bearing a chloro group on the Ph group (R^2), also gave disulfide **5d** in high yield (entry 4).

Because it was difficult to isolate 2-indolyl sulfides **4** under ordinary workup conditions, in situ transformation of the stannylthio group of **4** in one pot was attempted. Thus, the stannylthio group of 2-indolyl sulfide **4a** was readily transformed to alkylthio (**6**), 2-pyridylthio (**7**), and acylthio groups (**8**) in good yields (Scheme 3).[8]

Scheme 3. Transformation of the Tributylthio Group of Indole Derivative **4a**



In summary, we have achieved effective and unprecedented generation of 1,5-dipoles from *o*-stannylmethylated thioanilides via 1,6-stannatropy and their cyclization to afford indole derivatives in high yields. Based on this concept, the method was extended to the novel synthesis of tributyltin 2-indolyl sulfide derivatives from aryl isothiocyanates.

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Supporting Information Available: Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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