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# Indole synthesis from *N*-allenyl-2-iodoanilines under mild conditions mediated by samarium(II) diiodide†

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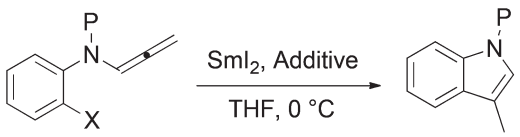
**A novel method for indole skeleton synthesis under mild conditions mediated by samarium(II) diiodide has been developed. The reaction of *N*-allenyl-2-iodoaniline derivatives with $SmI_2$ in the presence of HMPA and *i*-PrOH at 0 °C afforded indole derivatives in high yields.**

The indole skeleton is one of the most important frameworks of heterocyclic compounds and is widely found in pharmaceutical agents as well as bioactive natural products.[1] The synthesis of indole derivatives has been a central theme in organic synthesis, and numerous studies on the synthesis have been published.[2] Larock,[3] Castro,[4] Gelpke,[5] Ma,[6] Fuwa[7] and others have reported the reaction of 2-iodoaniline derivatives promoted by a transition-metal catalyst. On the other hand, Fukuyama[8] demonstrated an indole synthesis that proceeded under radical cyclisation conditions using tributyltin hydride from 2-isocyanostyrene derivatives or 2-alkenylthioanilides. However, there are a few practical and mild procedures that fulfilled all the conditions of low temperature, short reaction time and high yield for the construction of the indole skeleton. Acid and/or heat, which are the general conditions in the hitherto reported syntheses of indole derivatives, often cause significant difficulties in purification and/or decomposition of the starting material.[9]

Since Kagan's report on a simple method for the preparation of samarium(II) diiodide ($SmI_2$),[10] $SmI_2$ has been regarded as an important reductant for versatile single electron transfer (SET) reactions in the organic synthesis due to its diverse properties, such as low toxicity, easy preparation, tunable reactivity by changing additives, and usefulness under mild reaction conditions.[11] Recently, we have reported a $SmI_2$-mediated spirocyclisation that proceeds by the addition of a ketyl radical and/or an aryl radical onto an aromatic ring.[12] On the basis of that study, we turned our attention to a $SmI_2$-mediated cyclisation that involves the intramolecular addition reaction of an aryl radical with an allene group for the construction of an indole skeleton. Whereas a few $SmI_2$-mediated intramolecular and intermolecular coupling reactions of the ketyl radical with allenes have been reported,[13] as far as we know, the $SmI_2$-mediated intramolecular coupling of aryl radicals with allenes has not been studied.[14] In this communication, we describe a novel indole skeleton synthesis that is carried out under mild radical reaction conditions mediated by $SmI_2$.

We selected allenylanilines **1** (X = I or Br) as the starting material for indole synthesis. First, we investigated various protecting groups of the nitrogen atom and a series of reaction conditions (Table 1). On performing the reaction of tosyl-pro-

**Table 1** Screening for a variety of reaction conditions




**1a-d** **2a-c**

| Entry | Starting material | P | X | $SmI_2$ (equiv.) | Additive | Yield[a] (%) 2 | 1 |
|---|---|---|---|---|---|---|---|
| 1 | **1a:** | Ts | I | 5.0 | HMPA, *i*-PrOH | **2a:** 0 | **1a:** 72 |
| 2 | **1a:** | Ts | I | 8.0 | HMPA, *i*-PrOH | **2a′:** 71[b] | 0 |
| 3 | **1a:** | Ts | I | 5.0 | LiBr | **2a:** 0 | **1a:** 72 |
| 4 | **1b:** | Ac | I | 5.0 | HMPA | **2b:** 35 | 0 |
| 5 | **1b:** | Ac | I | 5.0 | HMPA, *i*-PrOH | **2a′:** 47[b] | 0 |
| 6 | **1c:** | Boc | I | 5.0 | HMPA | **2c:** 84 | 0 |
| 7 | **1c:** | Boc | I | 5.0 | HMPA, *i*-PrOH | **2c:** 93 | 0 |
| 8 | **1c:** | Boc | I | 3.8 | HMPA, *i*-PrOH | **2c:** 90 | 0 |
| 9 | **1c:** | Boc | I | 2.6 | HMPA, *i*-PrOH | **2c:** 88 | 0 |
| 10 | **1d:** | Boc | Br | 5.0 | HMPA, *i*-PrOH | **2c:** 35 | **1d:** 22 |
| 11 | **1c:** | Boc | I | 5.0 | DMPU, *i*-PrOH | **2c:** 57 | **1c:** 12 |

[a] Isolated yield. [b] Only deprotected indole **2a′**: (P = H) was obtained. HMPA = hexamethylphosphoramide, DMPU = *N*,*N*-dimethylpropylene urea.

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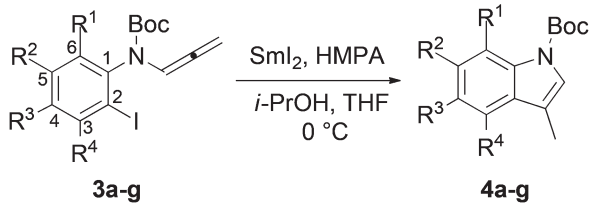
tected **1a** (X = I) with $SmI_2$ (5.0 equiv.) using HMPA and *i*-PrOH as additives, we recovered the starting material **1a** without the desired indole product **2a** (entry 1). When 8.0 equivalents of $SmI_2$ were used, the deprotected indole **2a′** (P = H) was obtained in 71% yield.[15] Undaunted by our unsatisfactory result, we examined the reaction in the presence of alkali metal salts,[16] according to our previous report that used LiBr instead of HMPA and *i*-PrOH to improve the yield and selectivity.[11] However, LiBr was not an effective additive in this cyclisation reaction (entry 3). Then, we attempted to perform the reaction of acetyl-protected allenylaniline **1b** (X = I) with HMPA as the additive and obtained the desired indole **2b** in 35% yield (entry 4). In contrast, the use of HMPA and *i*-PrOH as additives gave deprotected indole **2a′** in 47% yield (entry 5). We next examined the reaction of Boc-protected allenylaniline **1c** (X = I) with HMPA and obtained only **2c** in good yield (entry 6). When the reaction of Boc-protected allenylaniline **1c** was conducted in the presence of HMPA and *i*-PrOH, the reaction was completed within 5 min at 0 °C to afford indole **2c** in a remarkable 93% yield (entry 7). This result is in good accordance with our previous finding that the formation of spirocycles was promoted by the addition of *i*-PrOH to trap the anionic intermediate generated by further SET to the unstable radical intermediate.[12] It was found that reducing the amount of $SmI_2$ led to slightly low yields of indole **2c** and the use of 5.0 equivalents of $SmI_2$ gave indole **2c** in the highest yield (entries 7–9). When allenylaniline **1d** with Br as the substituent instead of I was used as the starting material, the cyclized product **2c** was afforded in 35% yield together with the recovery of the unchanged starting material **1d** in 22% yield. This indicates that the $SmI_2$-mediated SET to **1c** with an iodine atom to generate an aryl radical is more efficient than the $SmI_2$-mediated SET to **1d** with a bromide atom (entry 7 *vs.* 10). It was also found that DMPU, which is known as a substitute for HMPA,[17] did not work as well as HMPA in this cyclisation reaction (entry 7 *vs.* 11).

Next, we investigated the electronic effect of the substituent on the benzene ring (Table 2). Exposure of the starting material substituted at the 4-position with an electron-donating group such as a methyl or a methoxy group to the optimum reaction conditions ($SmI_2$/HMPA/*i*-PrOH) gave indoles **4a** and **4b** in good yields (entries 1 and 2). Moreover, the reaction of the starting material having an electron-withdrawing group, such as a chlorine which has the mesomeric π-donor character or a *N*,*N*-dimethylaminocarbonyl group, afforded cyclised products **4c** and **4d** in 74% and 21% yields, respectively (entries 3 and 4). The reaction of 6-methoxy-substituted analogue **3e** afforded indole **4e** in almost the same yield as that of the starting material **3b** bearing a methoxy group at the 4-position (entry 5 *vs.* 2). On the other hand, a methoxy substituent at the 5-position appreciably enhanced the yield of **4f** (entry 6). In addition, the reaction of 3-methoxy-substituted analogue **3g** gave indole **4g** in a slightly low yield compared with the other reactions. This would be explained by the steric interaction between the allene group and the methoxy group in the cyclisation. Considering those results, the electronic

**Table 2** Effect of the substituent on the benzene ring[a]




**3a-g** **4a-g**

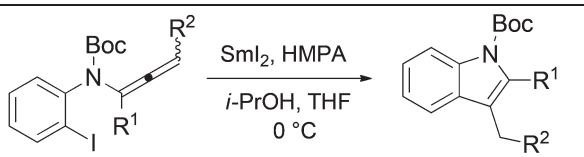
| Entry | Starting material | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **3a:** | H | H | Me | H | **4a:** 82 |
| 2 | **3b:** | H | H | OMe | H | **4b:** 80 |
| 3 | **3c:** | H | H | Cl | H | **4c:** 74 |
| 4 | **3d:** | H | H | $CONMe_2$ | H | **4d:** 21 |
| 5 | **3e:** | OMe | H | H | H | **4e:** 79 |
| 6 | **3f:** | H | OMe | H | H | **4f:** 89 |
| 7 | **3g:** | H | H | H | OMe | **4g:** 73 |

[a] All reactions were carried out in THF using $SmI_2$ (5.0 equiv.), *i*-PrOH (2.0 equiv.), and HMPA (18.0 equiv.) at 0 °C. [b] Isolated yield.

density on the aromatic ring would be an important factor for the samarium(II)-mediated cyclisation onto an allene group.

Then, to explore the substituent effect on the allene group, we prepared starting materials **5a–d** having substituents on the allene group at the α- or γ-position (Table 3). Unfortunately, the reaction of **5a** bearing a methyl group at the distal position of the allene moiety under the optimum reaction conditions led to a low yield of **6a** (entry 1). In contrast, *tert*-butyl-substituted **5b** produced **6b** in good yield under identical reaction conditions (entry 2). This is probably due to the instability of the allene moiety of **5a** under the reaction conditions.[18] Among the many methods that have been developed for the synthesis of indoles, few practical and mild methods are available for the formation of 2,3-disubstituted indoles.[9] We expect that our method would be applicable to the synthesis of 2,3-disubstituted indoles. The reaction of **5c** with a TMS group at

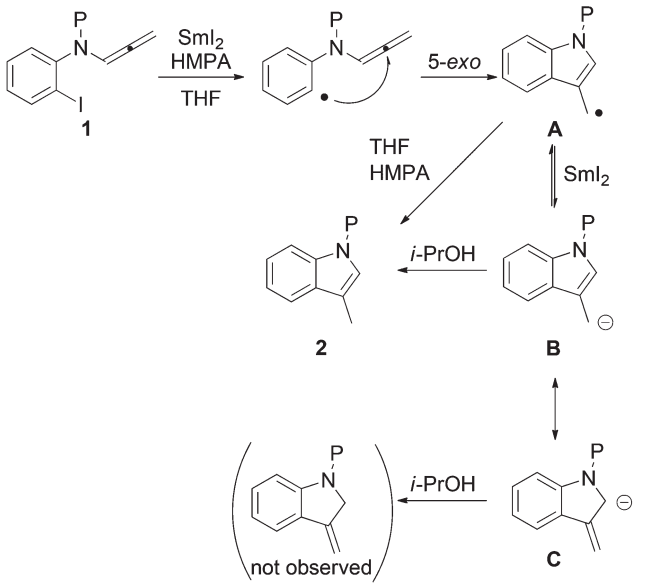
**Table 3** Effect of the substituent on the allene group[a]




**5a-d** **6a-d**

| Entry | Starting material | $R^1$ | $R^2$ | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **5a:** | H | Me | **6a:** 27 |
| 2 | **5b:** | H | *t*-Bu | **6b:** 77 |
| 3 | **5c:** | TMS | H | **6c:** 93 |
| 4 | **5d:** | Bn | H | **6d:** 99 |

[a] All reactions were carried out in THF using $SmI_2$ (5.0 equiv.), *i*-PrOH (2.0 equiv.), and HMPA (18.0 equiv.) at 0 °C. [b] Isolated yield.




**Scheme 1** Plausible reaction mechanism.

the proximal position of the allene group afforded 2,3-disubstituted indole **6c** bearing a silicon functional group at the C2 position, which served as a potential precursor for further functionalization by palladium(0)-catalysed transformation, in high yield (entry 3).[7,19] Furthermore, the reaction of **5d** with the benzyl group at the proximal position of the allene group gave **6d** with a benzyl group at the C2 position in excellent yield (entry 4).

A plausible reaction mechanism for the samarium(II)-mediated aryl radical coupling reaction with an allene group is shown in Scheme 1. The $SmI_2$-mediated SET to the iodide of **1** generates an aryl radical that would undergo a 5-*exo*-type intramolecular cyclisation by attacking the aryl radical on the center carbon of the allene group to produce radical intermediate **A**. The following SET generates anion **B**, and protonation of **B** in the presence of *i*-PrOH would promote the equilibrium of SET between **A** and **B** to afford preferentially **B**. However, the compound produced by isomerization of **B** into **C** followed by protonation was not observed at all. The fact that the reactions in the absence of *i*-PrOH gave indole products in lower yields than those in the presence of *i*-PrOH indicates that *i*-PrOH facilitates the equilibrium of SET between **A** and **B**, by tapping this anionic intermediate.[12] According to the results of Inanaga, Curran, and Reiβig,[13,20] under the reaction conditions in the absence of a proton source, the direct conversion of intermediate **A** into indole **2** by abstracting a hydrogen from the solvent THF or the additive HMPA has to be taken into account as an alternative pathway.

## Conclusions

We have demonstrated a $SmI_2$-mediated cyclisation reaction of an aryl radical with an allene group in the presence of HMPA and *i*-PrOH for the facile and mild synthesis of a variety of indole derivatives. This method would also be an effective tool for the formation of 2,3-disubstituted indoles.

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