

A NEW METHOD FOR THE CONSTRUCTION OF INDOLE NUCLEUS

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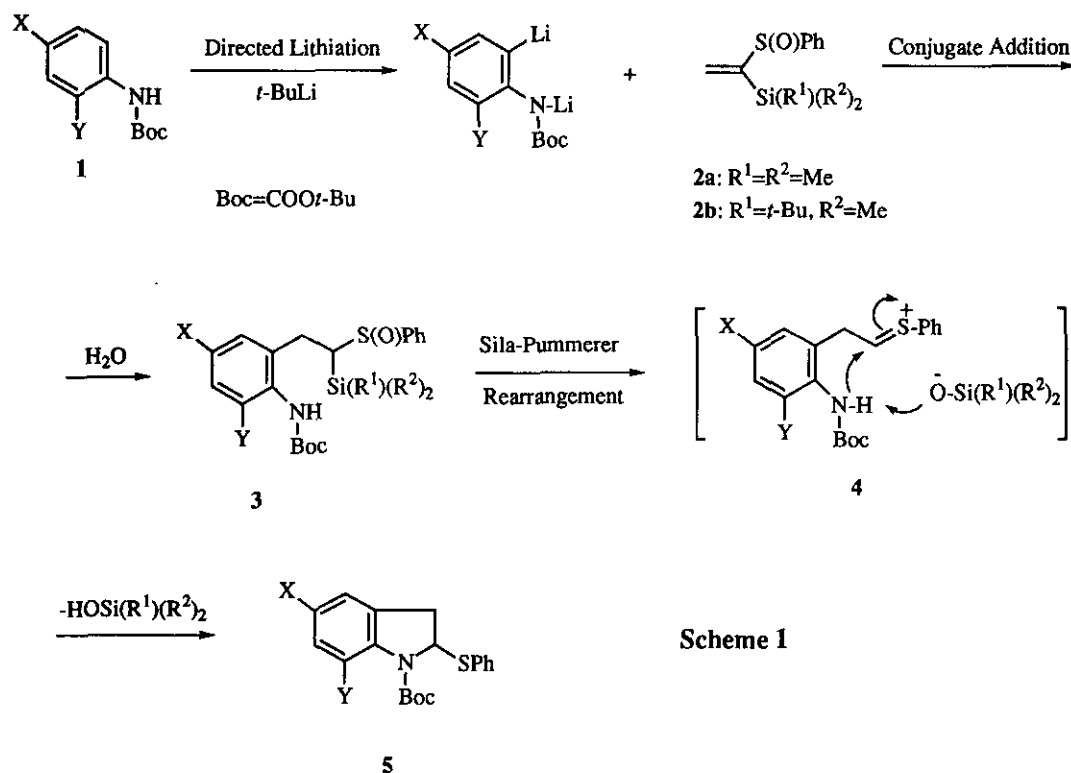
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Abstract- Directed lithiation of *N*-*tert*-butoxycarbonylanilines and subsequent reaction with 1-*tert*-butyldimethylsilyl-1-phenylsulfinylethene gave the conjugate addition products which, without isolation, were cyclized to 1-*tert*-butoxycarbonyl-2-phenylthioindolines under thermal sila-Pummerer reaction conditions.

Since the first synthesis of indole by von Baeyer in 1866,¹ a number of the synthetic methods for this heterocyclic system have been devised mainly due to significant biological activities of the indole natural products.² Although a variety of well-established classical indole syntheses are available,³ the newer syntheses, which focused on the regioselective construction of highly functionalized indoles, have been still actively investigated.⁴ In this communication, we wish to report a new synthesis of the indole ring system based on the consecutive directed lithiation-conjugate addition-sila-Pummerer rearrangement strategy.

The directed *ortho*-lithiation of *N*-*tert*-butoxycarbonylaniline (1a) has been reported by Muchowski and Venuti.⁵ The generality of this reaction has been demonstrated in the lithiation of a range of *N*-*tert*-butoxycarbonylanilines.⁶ On the other hand, the conjugate addition of organolithium and Grignard reagents to 1-trimethylsilyl-1-phenylsulfinylethene (2a) has been reported by Kanemasa, *et al.*⁷ By a combination of these two reactions, we obtained a following idea for the preparation of indole ring system (Scheme 1). Directed lithiation of *N*-*tert*-butoxycarbonylanilines (1) and subsequent reaction with the Michael acceptor (2a or 2b)

should afford the conjugate addition products (3). Thermolysis of 3 could cause sila-Pummerer rearrangement⁸ to generate the ion-pair intermediates (4) which might cyclize to 1-*tert*-butoxycarbonyl-2-phenylthioindolines (5) via initial proton abstraction from the acidic Boc-NH group by the silanoxide anion followed by addition to the sulfonium ion moiety.⁹ Based on this working hypothesis, following reactions were carried out.

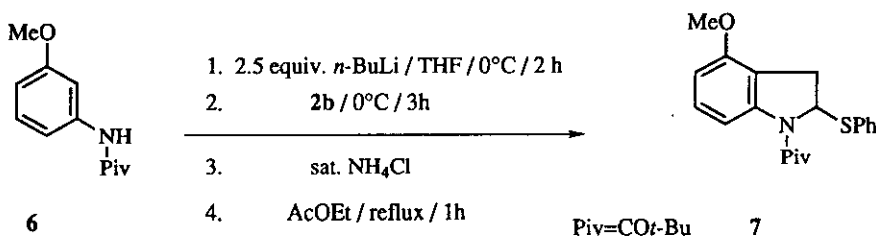


N-*tert*-Butoxycarbonylaniline (1a) was lithiated under the standard conditions⁵ (2.5 equiv. *t*-BuLi / THF / -78°C for 0.5 h, -20°C for 3 h) and then reacted with 1-*tert*-butyldimethylsilyl-1-phenylsulfinyethene (2b)¹⁰ (1.5 equiv.) at -20°C for 2 h. After quenching the reaction mixture with sat. NH₄Cl, the crude product was extracted with ethyl acetate and the extracted solution was refluxed for 1 h. After silica gel column chromatography (hexane-ethyl acetate 20:1), the indoline (5a) was isolated in 43% yield.¹¹ In a similar manner, a range of the substituted indolines (5b-h) were synthesized from the corresponding *N*-*tert*-butoxycarbonylanilines (1b-h) in moderate yields.^{12,13} The results were summarized in Table 1.

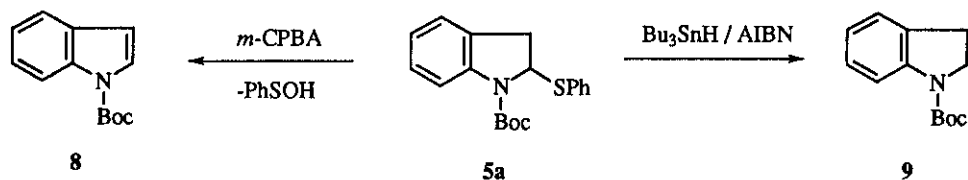
Table 1. Synthesis of 1-*tert*-Butoxycarbonyl-2-phenylthioindolines

Entry	<i>N</i> -(Boc)aniline	X	Y	1-(Boc)-2-(SPh)indoline	Yield(%)	mp(°C)
1	1a	H	H	5a	43	oil
2	1b	CH ₃	H	5b	34	62.5-63
3	1c	CF ₃	H	5c	47	oil
4	1d	MeO	H	5d	29	75-76
5	1e	Cl	H	5e	54	66-67
6	1f	F	H	5f	36	oil
7	1g	H	F	5g	42	68-68.5
8	1h	H	MeO	5h	27	107-108

When *N*-*tert*-butoxycarbonylanilines were not lithiated cleanly, such as the case of *N*-*tert*-butoxycarbonyl-3-methoxyaniline,^{6c} the corresponding *N*-pivaloylanilines¹⁴ could be employed alternatively. In this manner, 4-methoxy-2-phenylthio-1-pivaloylindoline (**7**) (mp 95-96°C) was prepared from 3-methoxy-*N*-pivaloylaniline (**6**) in 29% yield.



The phenylthio group of the indolines could be easily removed by oxidative elimination or by hydrogenolysis. For example, oxidation of **5a** with 1.1 equiv. of *m*-chloroperbenzoic acid in CH₂Cl₂ (ambient temp. / 5 h) caused spontaneous elimination of the resultant phenylsulfinyl group to give 1-*tert*-butoxycarbonylindole (**8**) in a quantitative yield. Hydrogenolysis of **5a** with Bu₃SnH¹⁵ in the presence of catalytic amount of AIBN (benzene / reflux / 1 h) provided 1-*tert*-butoxycarbonylindoline (**9**) in a quantitative yield.¹⁶



In summary, we have developed a new method for the construction of indole nucleus, which can be applicable for the regioselective synthesis of a variety of indoles and indolines substituted on the benzenoid ring. The desulfurized 1-*tert*-butoxycarbonyl-indoles and -indolines may be further functionalized at C-2 and C-7 positions, respectively, *via* the directed lithiation promoted by the remaining *tert*-butoxycarbonyl group.^{17,18} The deprotection of *tert*-butoxycarbonyl group can be effected under mild conditions.^{4c,17,18b,19} Thus, the procedure developed herein is quite useful for the preparation of selectively functionalized indole derivatives.

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9. A similar mechanism for cyclization of ω -carbamoylsulfoxides to α -phenylthiolactams under Pummerer rearrangement conditions has been reported, see: Y. Kita, O. Tamura, N. Shibata, and T. Miki, *Chem. Pharm. Bull.*, **1990**, *38*, 1473.
10. This compound was prepared from phenyl vinyl sulfide in two steps. α -Lithiation of phenyl vinyl sulfide (1.1 equiv. LDA / THF / -78°C / 2 h) followed by a reaction with *tert*-butyldimethylsilyl chloride (1.1 equiv., -78°C to ambient temp., overnight) gave 1-*tert*-butyldimethylsilyl-1-phenylthioethene in 77% yield after distillation (bp: $77\text{-}80^{\circ}\text{C}$ / 0.25 mmHg). The sulfide was oxidized with *m*-chloroperbenzoic acid (1.0 equiv. / CH_2Cl_2 / ambient temp. / 3h) and purified by silica gel column chromatography (hexane-ethyl acetate 5:1) to give **2b** in 87% yield.
11. When **2a** was used as a Michael acceptor, the yield of **5a** was only 22%. The poor yield may be due to the preferential recombination of less bulky trimethylsilanoxide anion with sulfonium cation in the intermediate (**4**) to give normal sila-Pummerer rearrangement product.
12. All new compounds were fully characterized by ^1H nmr (400 MHz), ir, and HRms.
13. In some cases (Entries 2, 6, and 8 in Table 1), the crude reaction products were treated with tetrabutylammonium fluoride in THF to remove the normal sila-Pummerer rearrangement products.
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