Preparation and Reactions of 1-(*tert*-Butyldimethylsilyl)-3-lithioindole. Regioselective Synthesis of 3-Substituted Indoles

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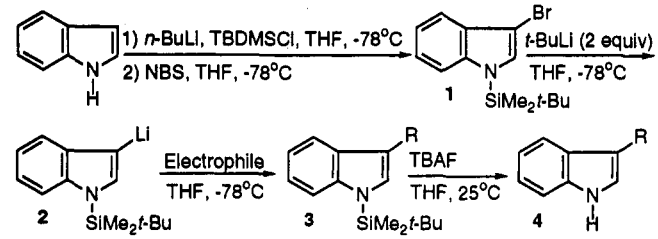
Summary: 1-(*tert*-Butyldimethylsilyl)-3-lithioindole (**2**) is prepared by metalation of the corresponding 3-bromo derivative **1** and efficiently reacts with electrophiles to give 3-substituted indoles **3** and **4**.

In spite of the inherent nucleophilic character of the 3-position in simple indoles or in indolylmagnesium halides, their reaction with electrophilic alkylating or acylating reagents usually gives competitive N- and 3-substituted products.[1] However, in contrast with the well-established preparation and abundant synthetic uses of a variety of N-protected 2-lithioindoles,[2,3] the chemistry of N-protected 3-lithioindoles has received very little attention and, even today, the use of these reagents has some inconveniences and limitations. In fact, only the benzenesulfonyl group has been used as N-protecting group in the generation of simple 3-lithioindole derivatives. 1-(Benzenesulfonyl)-3-lithioindole can be prepared at −100 °C by halogen–metal exchange with *t*-BuLi from the corresponding 3-iodo-[4] or 3-bromoindole[5] and efficiently reacts at this temperature with electrophiles, affording 3-substituted indoles.[4,5] At higher temperatures, however, it rearranges to the thermodynamically more stable (additional stabilization by coordination) 2-lithio isomer.[4a,5b,6] Other 3-lithioindole derivatives have been prepared by direct metalation of N-substituted indoles,[7] although this procedure requires the presence of an *ortho*-directing group at the indole 2-position.[8] The propensity of some *N*-(benzenesulfonyl)-3-lithioindoles to undergo a ring fragmentation to give 2-aminophenylacetylene derivatives[9] constitutes an additional inconvenience.

Scheme 1



In this context, we felt that the use of a bulky *tert*-butyldimethylsilyl group as the indole protecting group would avoid the undesired rearrangement observed in 1-(benzenesulfonyl)-3-lithioindoles because of the steric requirements of this substituent, which affords lateral protection of the 2-position, and its noncoordinating ability.[10] Moreover, the known facile tetraalkylammonium fluoride induced cleavage of trialkylsilyl substituents could constitute an additional advantage in the use of this indole protecting group.[11]

The required 3-bromo-1-(*tert*-butyldimethylsilyl)indole (**1**)[12] was prepared in 87% yield as a white solid in a one-pot reaction from indole, by silylation (*n*-BuLi, *tert*-butyldimethylsilyl chloride, −78 °C, THF) followed by bromination (NBS, 1 equiv, −78 °C, THF) (Scheme 1).[13] Compound **1** can be stored without appreciable decomposition for several months at temperatures below 0 °C

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(12) Compound **1** could not be crystallized since it easily decomposed on heating in solution. ^{1}H NMR ($CDCl_3$, 200 MHz): 0.60 (s, 6H, CH_3Si); 0.92 (s, 9 H, $(CH_3)_3C$); 7.17 (s, 1H, H-2); 7.20 (m, 2 H, H-5 and H-6); 7.48 (m, 1H, H-7), 7.54 (m, 1 H, H-4). ^{13}C NMR ($CDCl_3$, 50.3 MHz): −4.3 (CH_3Si); 19.1 (CSi); 26.0 (CH_3CSi); 93.7 (C-3); 114.1 (C-7); 119.2 (C-4); 120.6 (C-5); 122.6 (C-6); 129.8 (C-2); 130.0 (C-3a); 140.4 (C-7a).

(13) Careful chromatographic purification of the reaction mixture (silica gel; 1:1 CH_2Cl_2–hexane) in the preparation of **1** must be effected as soon as possible after workup in order to separate traces of contaminating 3-bromoindole (lower R_f), which promotes rapid decomposition.

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Table 1

entry	electrophile	R	yield (%) of 3	yield (%) of 4[a,b]
a	MeI	Me	95	85
b	EtI	Et	93	70
c	*n*-BuBr	*n*-Bu		61
d	$BrCH_2CH{=}CMe_2$[c]	$CH_2CH{=}CMe_2$		69[e]
e	$HCONMe_2$[d]	CHO		94
f	C_6H_5COCl[d]	COC_6H_5		84
g	$C_6H_5CO_2CH_3$[d]	COC_6H_5	69	58
h	$ClCO_2CH_3$[d]	CO_2CH_3	84	80
i	CO_2	CO_2H	94	
j	C_6H_5CHO	$CHOHC_6H_5$	67	
k	4-CHO-C_5H_4N	4-CHOH-C_5H_4N	55	
l	$ClSnMe_3$	$SnMe_3$	94	

[a] Overall yield after purification by column chromatography. [b] The NMR spectra compare well with the literature spectra (see supplementary material). [c] The 3-lithioindole **2** was converted into a cuprate by addition of 1 equiv of $CuBr{\cdot}SMe_2$. [d] In the reaction of **2** with acylating reagents (entries e–h) the best yields were obtained by reverse addition of the lithium derivative **2** to a THF solution of the electrophile at −78 °C. [e] An 85:15 mixture of **4d** and the isomer in which R is $CMe_2CH{=}CH_2$, respectively.

under an argon atmosphere. Treatment of a THF solution of **1** with 2 equiv of *t*-BuLi in hexane at −78 °C, followed by addition of MeI at −78 °C, afforded 1-(*tert*-butyldimethylsilyl)-3-methylindole (**3a**) in 95% yield. As a byproduct only small amounts of 1-(*tert*-butyldimethylsilyl)indole[2a] (**3**, R = H) were isolated, but not starting material **1**, thus indicating that the lithium derivative **2** is generated in an essentially quantitative manner. No compounds coming from methylation at the indole 2-position were observed. As expected, 1-(*tert*-butyldimethylsilyl)-3-lithioindole (**2**) proved to be a relatively stable species, which does not undergo either rearrangement to the 2-lithioindole isomer or ring fragmentation even *upon warming at room temperature*. Thus, similar yields of **3a** (90% yield, approximately) were obtained when the addition of MeI was effected either at 0 or 25 °C. In order to investigate the scope of the reaction, the 3-lithioindole derivative **2** was allowed to react with a wide variety of electrophilic reagents (Table 1), which included alkyl halides (entries a–d), acylating reagents (entries e–h), carbon dioxide (entry i), aromatic aldehydes (entries j, k), and trimethyltin chloride (entry l). The corresponding 3-substituted indoles were obtained in good to excellent yields. In some cases the initially formed N-protected indole **3** was not characterized but immediately desilylated with tetrabutylammonium fluoride (TBAF, 1 equiv, THF, 25 °C) to the corresponding 3-substituted indole **4** in good overall yield. As was observed in the preparation of **3a**, no rearrangement to the 2-lithio isomer was produced when the reaction of 3-lithioindole **2** with ethyl iodide was carried out at 0 °C; under these conditions the protected 3-ethylindole **3b** was obtained in 90% yield. The advantages of the *N*-silyl-3-lithioindole **2** due to the absence of both ring fragmentation and rearrangement to the 2-lithio isomer, the easy elimination of the protecting group, and the possibility of working at temperatures higher than −100 °C give to this reagent a considerable synthetic utility in the regioselective preparation of 3-substituted indoles.

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Supplementary Material Available: Experimental procedure for the preparation of **1**, general procedures for compounds **3** and **4**, and ^1H and ^{13}C NMR spectra for new compounds **1** and **3b,g–l** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.