

3-LITHIO-1-(TRIIISOPROPYLSILYL)INDOLE. PREPARATION AND REACTIONS WITH ELECTROPHILIC REAGENTS

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Abstract - 3-Lithio-1-(triisopropylsilyl)indole (**2**) is prepared by halogen-metal exchange from the corresponding 3-bromoindole and regioselectively reacts with a variety of electrophilic reagents to give 3-substituted indoles.

Organometallic indole derivatives are valuable intermediates for the preparation of substituted indoles.^{1,2} Whereas there are many studies about the generation and synthetic applications of *N*-protected 2-lithioindoles,³ their isomers, the 3-lithioindoles, have received less attention,^{1,4} probably due to the fact that, when operating with the usual benzenesulfonyl protecting group, *N*-sulfonylated 3-lithioindoles are prone to 3 → 2 migration of lithium⁵ and to ring fragmentation.⁶ We have recently reported that these inconveniences can be avoided by using the *tert*-butyldimethylsilyl protecting group and that 1-(*tert*-butyldimethylsilyl)-3-lithioindole efficiently reacts with electrophiles to regioselectively give 3-substituted indoles.⁷

These interesting results prompted us to study the reactivity of other 3-lithio-1-silylindoles bearing bulky alkyl groups on the silicon atom, in order to provide a more complete scope of their synthetic usefulness. We selected the triisopropylsilyl group,⁸ which has been recognized as one of the most effective trialkylsilyl groups in providing lateral protection of the pyrrole⁹ and indole¹⁰ 2-positions.

Silylation of the lithium salt of indole with triisopropylsilyl chloride, followed by addition of *N*-bromosuccinimide at -78°C , efficiently afforded (97% yield) the 3-bromoindole derivative (1) in a one-pot reaction. The 3-lithio-1-(triisopropylsilyl)indole (2) was generated from 1 by halogen-metal exchange with *tert*-butyllithium.

The 3-lithiated species (2) was allowed to react at -78°C with alkyl halides, prenyl bromide, benzoyl chloride, methyl benzoate, *N,N*-dimethylformamide, methyl chloroformate, benzaldehyde, carbon dioxide, and ethylene oxide (Table 1).¹¹ The reactions regioselectively led to the corresponding 3-substituted indoles in moderate to good yields. Neither 2-substituted indoles nor ring-fragmentation products were detected.

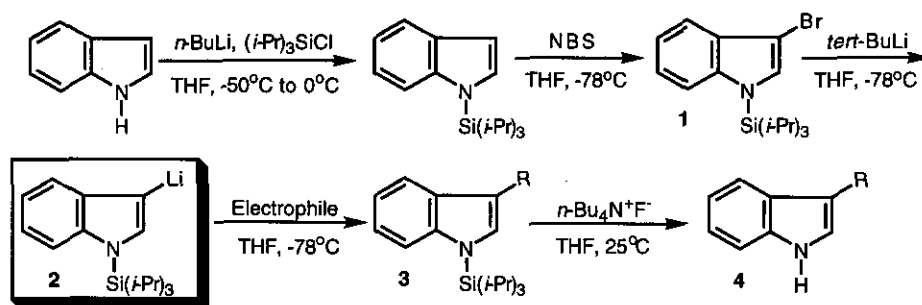


Table 1. Reactions of 3-Lithio-1-silylindole 2 with Electrophiles

	Electrophile	R	Yield of 3	Overall yield of 4
a	MeI	Me	90%	85%
b	EtI	Et	87%	69%
c	<i>n</i> -BuBr	<i>n</i> -Bu	80%	60%
d	BrCH ₂ CH=CMe ₂ ^a	CH ₂ CH=CMe ₂		60% ^b
e	HCONMe ₂ ^c	CHO	90%	85%
f	C ₆ H ₅ COCl ^c	COC ₆ H ₅	89%	85%
f	C ₆ H ₅ CO ₂ Me ^c	COC ₆ H ₅	65%	62%
g	ClCO ₂ Me ^c	CO ₂ Me	85%	70%
h	CO ₂	CO ₂ H	90%	
i	C ₆ H ₅ CHO	CHOHC ₆ H ₅	68%	^d
j	(CH ₂ CH ₂)O	CH ₂ CH ₂ OH	70%	62%

^aCuBr·SMe₂ (1 equiv) was added to the lithioindole (2). ^bThe isomer in which R is CMe₂CH=CH₂ was formed in 11% yield. ^cReverse addition of the lithium derivative to the electrophile. ^dPartial decomposition during purification by column chromatography.

Interestingly, when the reactions of **2** with methyl iodide and ethyl iodide were carried out at room temperature, the yields of the respective 3-alkylindoles were similar to those obtained when operating at -78°C , thus evidencing the stability of the 3-lithioindole (**2**). Both the steric requirements of the bulky silicon substituent and its non-coordinating ability prevent the undesirable rearrangement to the 2-lithio isomer. Compounds (**3**) were desilylated with tetrabutylammonium fluoride to give the corresponding *N*-unsubstituted indoles (**4**) in good overall yields.

Both the *tert*-butyldimethylsilyl- and triisopropylsilylindoles behave similarly in the lithiation of the respective 3-bromo derivatives and in the reactions of the resulting 3-lithioindole species with electrophiles. The main advantage in the use of the triisopropyl moiety lies in the greater stability of 1-(triisopropylsilyl)-3-acylindoles towards hydrolysis, thus allowing their isolation without partial desilylation during the work-up.

The results reported here confirm that 1-silylindoles bearing bulky alkyl groups on the silicon atom are useful and versatile starting materials for the regioselective lithiation at the indole 3-position and for the synthesis of a wide range of 3-substituted indoles. The syntheses of 3-alkylindoles and tryptophol are of particular interest.

EXPERIMENTAL SECTION

General: Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C -nmr spectra were recorded in CDCl_3 solution on a Varian Gemini 300 instrument. Chemical shifts are expressed in parts per million relative to internal TMS. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04-0.06 mm). Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

3-Bromo-1-(triisopropylsilyl)indole (1). To a solution of indole (4.0 g, 34 mmol) in anhydrous THF (140 ml) at -78°C was slowly added a solution of *n*-BuLi in hexane (23.4 ml of a 1.6 M solution, 37 mmol), and the temperature was raised to -10°C . After 15 min the reaction mixture was cooled to -50°C , and a solution of $(i\text{-Pr})_3\text{SiCl}$ (8.0 ml, 38 mmol) in THF (30 ml) was added

dropwise. After stirring at 0°C for 3 h the temperature was lowered to -78°C, and freshly crystallised *N*-bromosuccinimide (6.1 g, 34 mmol) was added. After 2 h the temperature was raised to 25°C, and hexane (100 ml) and pyridine (1 ml) were added. The resulting suspension was filtered through a Celite pad, and the filtrate was evaporated. The crude residue was chromatographed on silica gel (hexane) to give 11.7 g (97%) of 3-bromo-1-(triisopropylsilyl)indole (1) as a colourless solid. $^1\text{H-Nmr}$ (CDCl_3) δ 1.13 (d, $J=7.5$ Hz, 18H, CH_3), 1.67 (h, $J=7.5$ Hz, 3H, CH), 7.19 (m, 2H, H-5 and H-6), 7.24 (s, 1H, H-2), 7.48 (m, 1H, H-7), 7.57 (m, 1H, H-4); $^{13}\text{C-nmr}$ (CDCl_3 , 75 MHz) δ 12.8 (CH), 18.0 (CH_3), 93.6 (C-3), 114.1 (C-7), 119.1 (C-4), 120.6 (C-5), 122.5 (C-6), 129.7 (C-2), 130.0 (C-3a), 140.2 (C-7a); mp 38-40°C. Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{NBrSi}$: C, 57.94; H, 7.44; N, 3.97; Br, 22.68. Found: C, 57.91; H, 5.72; N, 4.02; Br, 22.93.

Generation of 3-Lithio-1-(triisopropylsilyl)indole (2) and General Procedure for the Preparation of 3-Substituted Indoles: 3-Methyl-1-(triisopropylsilyl)indole (3a). A solution of *tert*-BuLi (2.1 ml of a 1.7 M solution in pentane, 3.6 mmol) was slowly added at -78°C to a solution of 3-bromoindole (1) (570 mg, 1.6 mmol) in anhydrous THF (10 ml), and the mixture was stirred under argon atmosphere for 10 min. To the resulting 3-lithioindole (2) was added at -78°C a solution of methyl iodide (0.2 ml, 3.2 mmol) in THF (3 ml), and the stirring was continued for 15 min. Then the temperature was raised to 25°C, and the resulting mixture was poured into a cold saturated sodium carbonate solution and extracted with CH_2Cl_2 . The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated. Column chromatography on silica gel (hexane) afforded compound (3a) (418 mg, 90%). $^1\text{H-Nmr}$ (CDCl_3) δ 1.13 (d, $J=7.5$ Hz, 18H, $(\text{CH}_3)_2\text{CH}$), 1.68 (h, $J=7.5$ Hz, 3H, CH), 2.32 (s, 3H, CH_3Ind), 7.00 (s, 1H, H-2), 7.12 (m, 2H, H-5 and H-6), 7.46 (m, 1H, H-7), 7.55 (m, 1H, H-4); $^{13}\text{C-nmr}$ (CDCl_3 , 75 MHz) δ 10.5 (CH_3Ind), 13.5 (CH), 18.9 [$(\text{CH}_3)_2\text{CH}$], 114.0 (C-3), 114.4 (C-7), 119.3 (C-4), 119.8 (C-5), 121.9 (C-6), 129.0 (C-2), 132.5 (C-3a), 141.9 (C-7a). Anal. Calcd for $\text{C}_{18}\text{H}_{29}\text{NSi}$: C, 75.19; H, 10.17; N, 4.87. Found: C, 75.42; H, 10.29; N, 4.88.

General Procedure for the Desilylation: 3-Methylindole (4a). Operating as above, from 3-bromoindole (1) (400 mg, 1.14 mmol) was obtained a crude residue, which was dissolved in THF

(10 ml), and a solution of TBAF (1.4 ml of a 1 M solution in THF) was added. The mixture was stirred for 10 min at 25°C, poured into saturated aqueous sodium carbonate, and extracted with CH₂Cl₂. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a residue which, after column chromatography (1:3 CH₂Cl₂-hexane), afforded 3-methylindole (**4a**) (223 mg, 85%) as a white solid.

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11. All compounds were identified by their spectroscopic data (ir, ^1H - and ^{13}C -nmr) and elemental analysis or by comparison with authentic samples.

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