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

Mercedes Amat,* Swargam Sathyanarayana, Sabine Hadida, and Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

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 lithium[5] 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 pyrrole[9] and indole[10] 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.

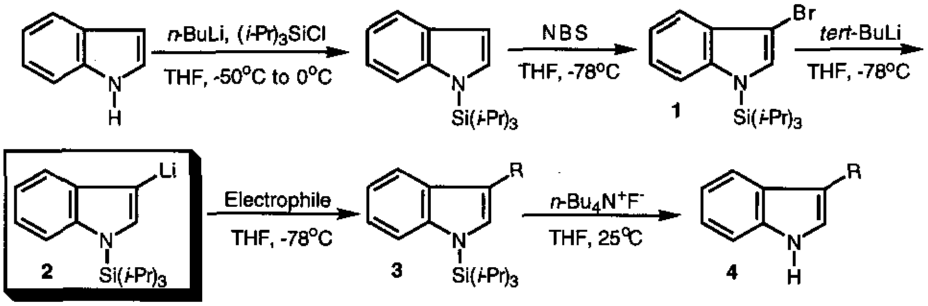

Table 1. Reactions of 3-Lithio-1-silylindole 2 with Electrophiles

	Electrophile	R	Yield of **3**	Overall yield of **4**
a	MeI	Me	90%	85%
b	EtI	Et	87%	69%
c	*n*-BuBr	*n*-Bu	80%	60%
d	$BrCH_2CH{=}CMe_2$[a]	$CH_2CH{=}CMe_2$		60%[b]
e	$HCONMe_2$[c]	CHO	90%	85%
f	C_6H_5COCl[c]	COC_6H_5	89%	85%
f	$C_6H_5CO_2Me$[c]	COC_6H_5	65%	62%
g	$ClCO_2Me$[c]	CO_2Me	85%	70%
h	CO_2	CO_2H	90%	
i	C_6H_5CHO	$CHOHC_6H_5$	68%	*d*
j	$(CH_2CH_2)O$	CH_2CH_2OH	70%	62%

[a] $CuBr.SMe_2$ (1 equiv) was added to the lithioindole (**2**). [b] The isomer in which R is $CMe_2CH{=}CH_2$ was formed in 11% yield. [c] Reverse addition of the lithium derivative to the electrophile. [d] Partial 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 requeriments 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 trisopropyl 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. ^{1}H 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 $(i\text{-Pr})_3SiCl$ (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}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}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 $C_{17}H_{26}NBrSi$: 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$_2$Cl$_2$. 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}H-Nmr (CDCl$_3$) δ 1.13 (d, *J*= 7.5 Hz, 18H, (C*H*$_3$)$_2$CH), 1.68 (h, *J*= 7.5 Hz, 3H, CH), 2.32 (s, 3H, C*H*$_3$Ind), 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}C-nmr (CDCl$_3$, 75 MHz) δ 10.5 (CH$_3$Ind), 13.5 (CH), 18.9 [(*C*H$_3$)$_2$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 $C_{18}H_{29}NSi$: 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 CH_2Cl_2. 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 CH_2Cl_2-hexane), afforded 3-methylindole (**4a**) (223 mg, 85%) as a white solid.

ACKNOWLEDGMENTS

Financial support from the DGICYT, Spain (project PB94-0214) and the "Comissionat per a Universitats i Recerca", Generalitat de Catalunya (Grant SGR95-0428) is gratefully acknowledged. S.S. thanks the CICYT, Spain, for providing a postdoctoral fellowship.

REFERENCES AND NOTES

1. R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, Chapter 1; R. A. Jones, "Comprehensive Heterocyclic Chemistry", Vol. 4, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, pp. 201-312; R. J. Sundberg, "Progress in Heterocyclic Chemistry", Vol. 7, ed. by H. Suschitzky and E. F. V. Scriven, Pergamon, Oxford, 1995, Chapter 5, part 2, and previous volumes in this series.
2. For recent references, see: M. Somei and T. Kobayashi, *Heterocycles*, 1992, **34**, 1295; W.G. Gribble, D. J. Keavy, D. A. Davis, M. G. Saulnier, B. Pelcman, T. C. Barden, M. P. Sibi, E. R. Olson, and J. J. BelBruno, *J. Org. Chem.*, 1992, **57**, 5878; T. Sakamoto, Y. Kondo, N. Takazawa, and H. Yamanaka, *Heterocycles*, 1993, **36**, 941; M. Amat, S. Hadida, and J. Bosch, *Tetrahedron Lett.*, 1994, **35**, 793; S. S. Labadie and E. Teng, *J. Org. Chem.*, 1994, **59**, 4250. See also references cited therein.
3. R. J. Sundberg and H. Russell, *J. Org. Chem.*, 1973, **38**, 3324; M. Gharpure, A. Stoller, F. Bellamy, G. Firnau, and V. Snieckus, *Synthesis*, 1991, 1079, and references cited therein.

4. Very recently, the preparation of 1-(benzenesulfonyl)-3-indolylmagnesium bromide and its reaction with electrophiles to give 3-substituted indoles has been reported: Y. Kondo, A. Yoshida, S. Sato, and T. Sakamoto, *Heterocycles*, 1996, **42**, 105.
5. M. G. Saulnier and G. W. Gribble, *J. Org. Chem.*, 1982, **47**, 757.
6. G. W. Gribble and M. G. Saulnier, *J. Org. Chem.*, 1983, **48**, 607.
7. M. Amat, S. Hadida, S. Sathyanarayana, and J. Bosch, *J. Org. Chem.*, 1994, **59**, 10.
8. C. Rücker, *Chem. Rev.*, 1995, **95**, 1009.
9. B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis, and J. M. Muchowski, *J. Org. Chem.*, 1990, **55**, 6317, and references cited therein.
10. P. J. Beswick, C. S. Greenwood, T. J. Mowlem, G. Nechvatal, and D. A. Widdowson, *Tetrahedron*, 1988, **44**, 7325; M. Iwao, *Heterocycles*, 1993, **36**, 29.
11 All compounds were identified by their spectroscopic data (ir, ^{1}H- and ^{13}C-nmr) and elemental analysis or by comparison with authentic samples.

Received, 23rd April, 1996