

**DIRECTED LITHIATION OF 1-TRISOPROPYLSILYLGRAMINE.
A SHORT ACCESS TO 3,4-DISUBSTITUTED INDOLES**

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Abstract- 1-Triisopropylsilylgramine was lithiated regioselectively at C-4 by treatment with *t*-BuLi in ether at 0 °C for 1 h. The lithiated species was trapped with a variety of electrophiles to furnish 4-functionalized gramine derivatives in good yields. Replacement of the triisopropylsilyl protecting group by a methyl group resulted in C-2 selective lithiation under the similar reaction conditions.

Due to the pronounced pharmacological activities of ergot alkaloids,¹ the practical syntheses of 4-substituted indoles have been long desired as the starting points for these compounds.² The direct functionalization of indole derivatives at C-4, however, is relatively difficult due to high reactivity of pyrrole moiety. The commercially available gramine³ [3-(dimethylaminomethyl)indole] has been widely used for functionalization of indole at C-3 side chain by nucleophilic substitution of dimethylamino group.⁴ Therefore, if gramine could be functionalized at C-4, this compound should serve as an ideal starting material for the preparation of 3,4-disubstituted indoles related to ergot alkaloids. In this communication, we wish to report the C-4 selective functionalization of gramine *via* the directed lithiation⁵ of 1-triisopropylsilylgramine (**1**) in which the dimethylaminomethyl group promotes the lithiation and the bulky triisopropylsilyl group prevents undesirable C-2 lithiation.⁶

The compound (**1**) was prepared from gramine by metalation with *n*-BuLi (1.05 equiv. / THF / -78°C / 1 h) followed by silylation with triisopropylsilyl chloride (1.1 equiv. / -78°C / 4 h) in 96% yield after Kugelrohr distillation (bp 140°C / 0.1 mmHg). Treatment of an ethereal solution of **1** with 1.2 equiv. of *t*-BuLi (15 min at -78°C and then 1 h at 0°C) followed by quenching with MeOD at -78°C recovered the deuterated gramine (**3a**) in

88 % yield after chromatographic purification. The 400 MHz ^1H nmr spectrum of this product showed >95% deuterium incorporation at C-4 and no evidence of C-2 deuteration. In this reaction, however, 2-triisopropylsilylgramine (**4**) was isolated as a by-product in 10% yield. This compound must be formed *via* C-2 lithiation of **1** followed by rapid N to C migration^{9c} of triisopropylsilyl group under the lithiation conditions. When **1** was lithiated at -78°C (1.2 equiv. of *t*-BuLi / ether / 2 h), **4** was not formed (MeOD quenching). However, deuterium incorporation in the recovered **1** was only 10% at C-4. Thus the lithiation at 0°C is essential for the efficient generation of the lithiated species (**2**). Using the lithiation conditions thus established, **2** was then reacted with a variety of electrophiles. The results were summarized in Table 1. In all cases, the expected 4-substituted gramine derivatives (**3**) were obtained in good yields.⁷

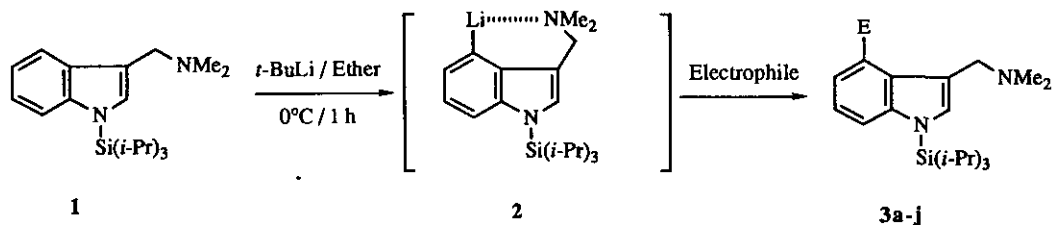
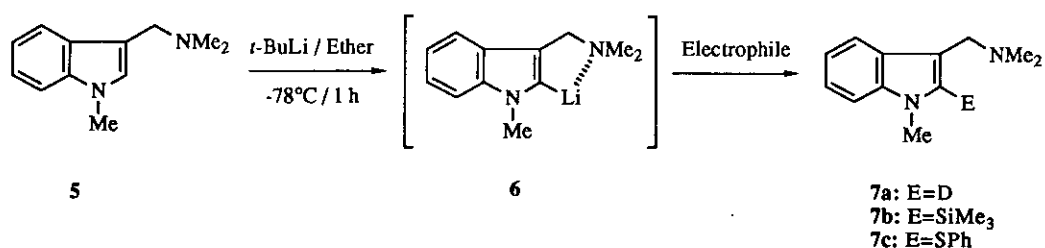


Table 1. Synthesis of 4-Substituted Gramines *via* Directed Lithiation of 1-Triisopropylsilylgramine

Entry	Electrophile	Product	E	Yield (%) ^a	mp ($^\circ\text{C}$)
1	MeOD	3a	D	88	oil
2	Me_3SiCl	3b	Me_3Si	82	oil
3	Bu_3SnCl	3c	Bu_3Sn	78	oil
4	PhSSPh	3d	PhS	70	85-86
5	I_2	3e	I	58	oil
6	$\text{BrCH}_2\text{CH}_2\text{Br}$	3f	Br	68	oil
7	Cl_3CCCl_3	3g	Cl	65	oil
8	$\text{N}_3\text{CH}_2\text{SiMe}_3$ ^b	3h	NH_2	80	97-97.5
9	DMF	3i	CHO	57	oil
10	$\text{Me}_2\text{C}=\text{CHCHO}$	3j	$\text{Me}_2\text{C}=\text{CHCH}(\text{OH})$	82	oil

^a Isolated yield after alumina column chromatography. ^b See reference 8.

In order to assess the steric requirement of triisopropylsilyl group,^{6b-c,9} lithiation of 1-methylgramine (**5**)¹⁰ was conducted. Treatment of an ethereal solution of **5** with 1.2 equiv. of *t*-BuLi at -78°C for 1 h followed by MeOD quenching provided C-2 deuterated compound (**7a**) in 93% yield (deuterium incorporation > 95%). This result clearly indicates that the methyl group is not large enough to prevent the preferential C-2 lithiation of the indole ring and the protection of indole nitrogen with bulky triisopropylsilyl group is essential for the success of C-4 lithiation. The lithiated species (**6**) reacted with Me₃SiCl and PhSSPh to give the corresponding C-2 substituted compounds (**7b**) (oil) and (**7c**) (mp 65-65.5°C) in 80% and 99% yields, respectively.⁷



In conclusion, we have devised a convenient procedure for C-4 functionalization of gramine *via* directed lithiation strategy. Most of the C-4 substituted gramines prepared in this work will be used as useful intermediates for the synthesis of more complex 3,4-disubstituted indole derivatives.¹¹ Application of this reaction for the short synthesis of ergot alkaloids is in progress in this laboratory.

Typical experimental procedure for the synthesis of 4-substituted gramines (3): Under an argon atmosphere, *t*-BuLi (1.5 M in pentane, 1.6 ml, 2.4 mmol) was added dropwise to a stirred solution of **1** (661 mg, 2.0 mmol) in dry ether (10 ml) at -78°C. After 15 min, dry ice-acetone bath was removed and the mixture was allowed to warm to 0°C (*ca.* 10 min). The reaction flask was then immersed in an ice-water bath and kept for 1 h. After cooling to -78°C, a solution of the appropriate electrophile (3.0 mmol) in dry ether (2 ml) was added. The solution was stirred for 1 h at -78°C and then allowed to warm to ambient temperature and quenched with water. After usual extractive workup (ether), the crude product was purified by alumina column chromatography using a mixture of hexane and ethyl acetate as an eluent.

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