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

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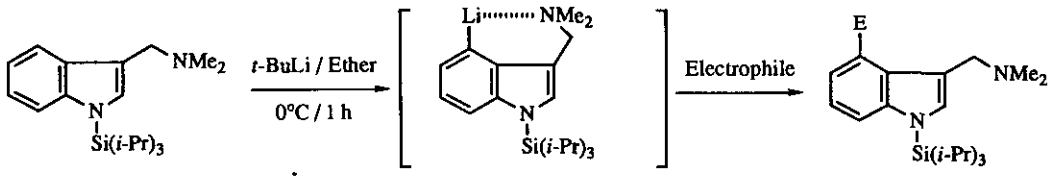
Abstract- 1-Triisopropylsilylgramine was lithiated regioselectively at C-4 by treatment with *t*-BuLi in ether at 0 °C for 1 h. The lithiated species was trapped with a variety of electrophiles to furnish 4-functionalized gramine derivatives in good yields. Replacement of the triisopropylsilyl protecting 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 gramine[3] [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 lithiation[5] 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 Kügelrohr 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 ^{1}H 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 triisopropylsily 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]



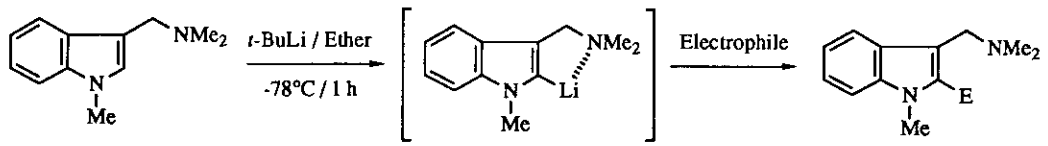
1 **2** **3a-j**

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

Entry	Electrophile	Product	E	Yield (%)[a]	mp (°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	$BrCH_2CH_2Br$	**3f**	Br	68	oil
7	Cl_3CCCl_3	**3g**	Cl	65	oil
8	$N_3CH_2SiMe_3$ [b]	**3h**	NH_2	80	97-97.5
9	DMF	**3i**	CHO	57	oil
10	Me_2C=CHCHO	**3j**	Me_2C=CHCH(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 Me_3SiCl 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]



5 **6** **7a:** E=D **7b:** E=$SiMe_3$ **7c:** E=SPh

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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Received, 27th July, 1992