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Methodology for the Efficient Synthesis of 3,4-Differentially Substituted Indoles. Fluoride Ion-induced Elimination-Addition Reaction of 1-Triisopropylsilylgramine Methiodides

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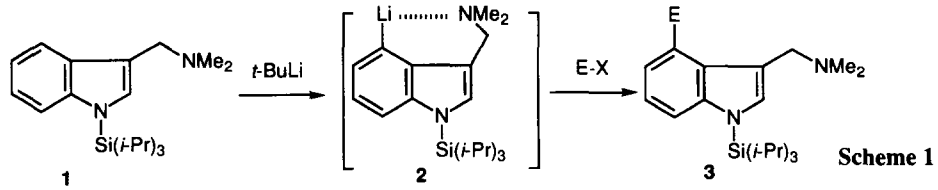
Abstract: 1-Triisopropylsilylgramine methiodide reacted smoothly with a variety of nucleophiles in the presence of tetrabutylammmonium fluoride to give 3-substituted indoles. The 3,4-disubstituted indoles were efficiently synthesized by sequential use of 4-selective lithiation of 1-triisopropylsilylgramine and this new substitution reaction.

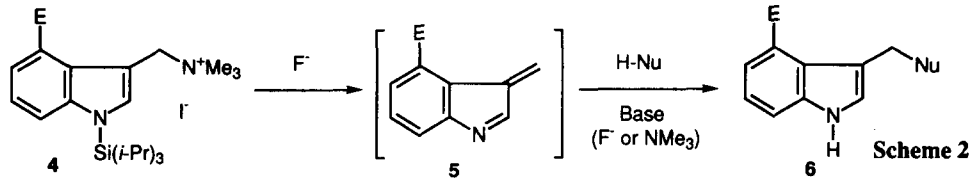
A number of biologically significant natural products such as ergot alkaloids,[2] teleocidins,[3] and some plant growth regulators[4] comprise a 3,4-disubstituted indole nucleus. However, straightforward synthesis of the indole derivatives having such substitution pattern from readily available starting materials is not so easy. Many research groups, therefore, have endeavored to develop new methodologies to access this class of compounds.[2,5] Recently, we have reported a potentially useful method for 4-selective functionalization of the indole ring based on directed lithiation of 1-triisopropylsilylgramine (**1**) (**Scheme 1**).[6] In this Letter, we describe a procedure for further functionalization of **3** at the C-3 side chain to produce 3,4-differentially substituted indoles.



Scheme 1

The logical approach[7] for this transformation may consist of two reaction steps: i) deprotection of the triisopropylsilyl group and ii) conventional gramine substitution reaction.[8] We envisaged, however, these processes could be accomplished in a single step by taking advantage of the inherent reactivities of 1-triisopropylsilylgramines. The nucleophilic substitutions of gramine derivatives have been believed to proceed *via* the elimination-addition mechanism passed through the 3-methylene-indolenine type intermediates.[8,9] We thought similar intermediates **5** might be easily generated from the methiodides **4** by 1,4-elimination triggered by the attack of the fluoride ion on the triisopropylsilyl group.[10] The reactive intermediates thus generated

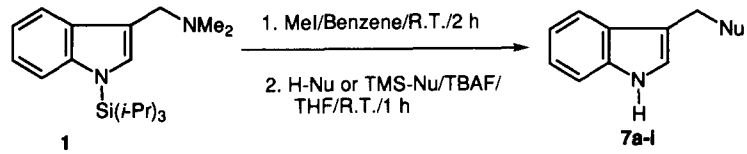
should be intercepted by nucleophiles, such as active methylene compounds, using the fluoride ion[11] and/or *in situ* generated trimethylamine as the base catalyst to give the 3,4-disubstituted indoles **6** (**Scheme 2**).



Scheme 2

At first, we tested this idea by using the 4-unsubstituted gramine **1** and a variety of nucleophiles. Thus, **1** was quaternized with iodomethane (2.0 equiv.) in benzene at room temperature for 2 hours to afford, after evaporation of the benzene, the methiodide as a white powder in an essentially quantitative yield. Tetrabutylammonium fluoride (TBAF) (1.5 equiv., 1.0M THF solution) was injected to the mixed suspension of the methiodide and an appropriate nucleophile in THF, and the resulting clear solution was stirred at room temperature for 1 hour. After usual workup and chromatographic purification, the substitution product was obtained in the yields shown in **Table 1**.

Table 1. Reaction of 1-Triisopropylsilylgramine Methiodide with Nucleophiles in the Presence of TBAF.

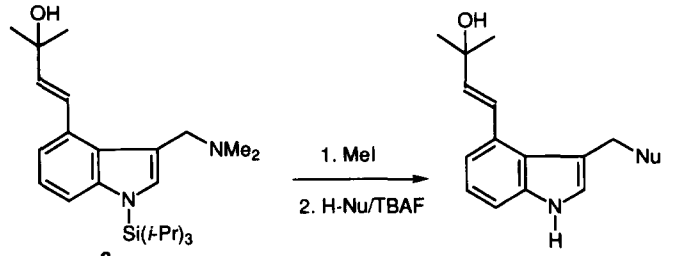


Entry	H-Nu or TMS-Nu (equiv.)	Product	Yield/%[a]	Mp/°C (Lit. Mp/°C)[ref.]
1	CH_3NO_2 (10.0)	**7a**	89	53-54 (54.0-55.0)[9]
2	CH_3COCH_2COOMe (10.0)	**7b**	97	oil
3	$CH_2(COOMe)_2$ (10.0)	**7c**	93	oil
4	$AcNHCH(COOEt)_2$ (1.1)	**7d**	95	144-145 (158-159)[9]
5	Phthalimide (1.1)	**7e**	93	181-183 (179-180)[13]
6	HSPh (1.5)	**7f**	97	84-85 (84)[14]
7	$HP(O)(OEt)_2$ (1.5)	**7g**	79	58-59 (61-62)[15]
8	TMS-CN[b] (1.5)	**7h**	91	oil
9	TMS-N_3[c] (3.0)	**7i**	79	oil

[a] Overall yield from **1**. [b] 3.0 equiv. of TBAF was used. [c] 4.5 equiv. of TBAF was used.

In the reaction with the active methylene compounds, such as nitromethane, methyl acetacetate, and dimethyl malonate, we used large excess (10.0 equiv.) of the nucleophiles in order to suppress the formation of dialkylated products.[12] Under these conditions, the monoalkylated compounds **7a-c** were obtained in excellent yields (Entries 1, 2, and 3). Diethyl acetaminomalonate also reacted to afford **7d** in excellent yield (Entry 4). Heteronucleophiles such as phthalimide, thiophenol, and diethyl phosphite reacted in good yields (Entries 5, 6, and 7). Trimethylsilyl cyanide and trimethylsilyl azide were successfully employed as cyanide and azide ion sources, respectively (Entries 8 and 9).

Based on the success of these reactions, the preparation of 3,4-disubstituted indoles of synthetic value was carried out subsequently. Thus, the compound **8**, which could be prepared from **1** in two steps,[16] was quaternized with iodomethane (2.0 equiv.) in benzene at room temperature overnight in 99% yield. The resulting methiodide was treated with TBAF in the presence of 10.0 equiv. of nitromethane to give **9a**, mp 105-106 °C, in 85% yield. This compound has been employed as the key intermediate in the syntheses of the ergot alkaloids, such as secoagroclavine[17] and aurantioclavine.[18] In a similar manner, the 3,4-disubstituted indole **9b**, mp 121-123 °C, was synthesized from **8** using 1.1 equiv. of diethyl (2,2,2-trichloroethoxycarbonyl)aminomalonate as a nucleophile in 92% yield. This compound has been converted to clavicipitic acid.[19]



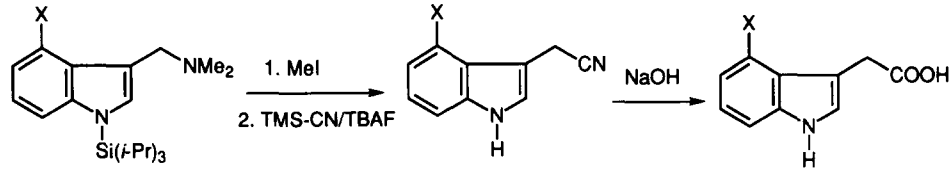
8

9a: Nu=CH_2NO_2

9b: Nu=C(TrocNH)$(COOEt)_2$

Scheme 3

As other examples, 4-halogenoindole-3-acetonitriles **11a-c** were synthesized from 4-halogeno-1-triisopropylsilylgramines **10a-c**, which were prepared by the directed lithiation of **1** in a single step,[6] and trimethylsilyl cyanide in good yields (**11a**: mp 134.5-135.5 °C, 89%; **11b**: mp 155-156°C, 85%; **11c**: mp 169.5-170 °C, 80%)[20] (**Scheme 4**). The nitrile **11a** was hydrolyzed (40%NaOH/MeOH/reflux/2h)[20] to a naturally occurring powerful plant growth hormone,[4a,c] 4-chloroindole-3-acetic acid (**12**), mp 186-188 °C, in 83% yield.



10a: X=Cl
10b: X=Br
10c: X=I

11a: X=Cl
11b: X=Br
11c: X=I

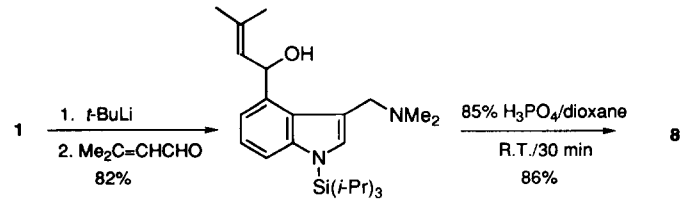
12: X=Cl

Scheme 4

In conclusion, we have devised an efficient procedure for the nucleophilic displacement of *N,N*-dimethylamino group of 1-triisopropylsilylgramines *via* the fluoride ion-induced elimination-addition reaction. This method is particularly useful for the preparation of 3,4-differentially substituted indoles by combinational use of the directed lithiation of 1-triisopropylsilylgramine **1**, as exemplified in the synthesis of **9a,b** and **11a-c**. We believe the methodology is widely applicable for the syntheses of biologically significant complex natural products having a 3,4-disubstituted indole nucleus.

References and Notes

1. Undergraduate student, Department of Marine Biochemistry, Faculty of Fisheries, Nagasaki University.
2. Ninomiya, I.; Kiguchi, T. ERGOT ALKALOIDS. In *The ALKALOIDS* ; Brossi, A. Ed.; Academic Press: San Diego, 1990; Vol. 38, pp.1-156.
3. Fujiki, H.; Sugimura, T. *Adv. Cancer Res.* **1987**, *49*, 223.
4. a) Marumo, S; Hattori, H.; Abe, H.; Munakata, K. *Nature* **1968**, *219*, 959; b)Marumo, S.; Abe, H.; Hattori, H.; Munakata, K. *Agric. Biol. Chem.* **1968**,*32*, 117; c) Böttger, M.; Engvild, K. C.; Soll, H. *Planta* **1978**, *140*, 89.
5. For reviews, see: a) Howell, D. C. *Tetrahedron* **1980**, *36*, 3123; b) Kozikowski, A. P. *Heterocycles* **1981**,*16*, 267; c) Somei, M. *Yuki Gosei Kagaku Kyokaishi* **1982**, *40*, 387; d) Natsume, M. *Yakugaku Zasshi* **1988**, *108*, 109; e) Somei, M. *Yakugaku Zasshi* **1988**, *108*, 361; f) Hegedus, L. F. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113. For recent studies, see: a) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395; b) Martin, S. F.; Liras, S. *J. Am. Chem. Soc.* **1993**, *115*, 10450; c) Nakagawa, K.; Somei, M. *Heterocycles* **1994**, *39*, 31; d) Ishibashi, H.; Akamatsu, S.; Iriyama, H.; Hanaoka, K.; Tabata, T.; Ikeda, M. *Chem. Pharm. Bull.* **1994**, *42*, 271; e) Yokoyama, Y.; Takahashi, M.; Takashima, M.; Kohno, Y.; Kobayashi, H.; Takaoka, K.; Shidori, K.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 832; f) Teranishi, K.; Hayashi, S.; Nakatsuka, S.; Goto, T. *Tetrahedron Lett.* **1994**, *35*, 8173; g) Tidwell, J. H.; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164; h) Barbey, S.; Mann, J. *SYNLETT* **1995**, 27.
6. Iwao, M. *Heterocycles* **1993**, *36*, 29.
7. Nettenkoven, M.; Psiorz, M.; Waldmann, H. *Tetrahedron Lett.* **1995**, *36*, 1425.
8. Brewster, J. H.; Eliel, E. L. *Org. React.* **1953**, *7*, 99.
9. Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941.
10. Fluoride ion-induced 1,4-elimination of [*o*-(α-(trimethylsilyl)alkyl)benzyl]trimethylammonium halides has been reported, see: Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609.
11. Li, W.-S.; Thottathil, J.; Murphy, M. *Tetrahedron Lett.* **1994**, *35*, 6591, and references cited therein.
12. For example, when 1.1 equiv. of nitromethane was used as a nucleophile, di(indol-3-ylmethyl)nitromethane was isolated in 46% yield, accompanied by **7a** (50%). For the dialkylation problem, see: references 8 and 9.
13. Mamaev, V. P.; Sedova, V. F. *Izv. Sibirsk. Otd. Akad. Nauk SSSR* **1961**, 142.
14. Poppelsdorf, F.; Holt, S. J. *J. Chem . Soc.* **1954**, 1124.
15. Torralba, A. F.; Myers, T. C. *J. Org. Chem.* **1957**, *22*, 972.
16. Compound **8** was synthesized by the procedure shown below.



17. Somei, M.; Yamada, F.; Karasawa, Y.; Kaneko, C. *Chem. Lett.* **1981**, 615.
18. Yamada, F.; Makita, Y.; Suzuki, T.; Somei, M. *Chem. Pharm. Bull.* **1985**, *33*, 2162.
19. Iwao, M., unpublished result. For the syntheses of clavicipitic acid, see: Somei, M.; Hamamoto, S.; Nakagawa, K.; Yamada, F.; Ohta, T. *Heterocycles* **1994**, *37*, 719, and references cited therein.
20. Somei, M.; Kizu, K.; Kunimoto, M.; Yamada, F. *Chem. Pharm. Bull.* **1985**, *33*, 3696.

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