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A CONVENIENT METHOD FOR THE SYNTHESIS OF UNSYMMETRICAL 3,4-DISUBSTITUTED PYRROLES

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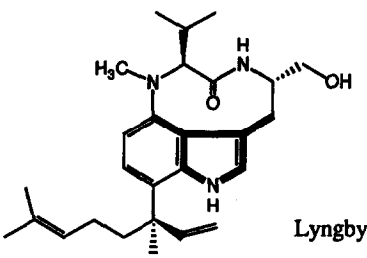
Abstract: *A simplified procedure for the synthesis of 3,4-dibromo-1-[tris(1-methylethyl)silyl]-1H-pyrrole (2) is described together with its sequential halogen-metal exchange chemistry to afford 3,4-disubstituted pyrroles.*

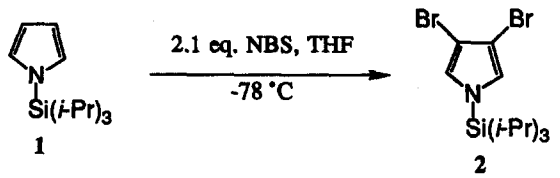
During efforts relating to the synthesis of analogues of the protein kinase C (PKC) activator,[1] lyngbyatoxin A, the need arose to prepare certain 3,4-disubstituted pyrroles as synthetic intermediates. Because electrophilic aromatic substitution reactions of pyrroles occur predominantly at the α-position, selective substitution at one or more of the β-positions has generally proven to be a more challenging synthetic task. Although 1-(phenylsulfonyl)-1*H*-pyrrole will undergo $AlCl_3$-catalyzed Friedel-Crafts acylation reactions at the 3-position, further electrophilic substitution at the 4-position of the 3-acylpyrrole has generally proven unsuccessful.[2] In most cases, the generation of 3,4-disubstituted pyrroles has required *de novo* synthetic approaches.[3]



Lyngbyatoxin A

3,4-Dibromo-1-[tris(1-methylethyl)silyl]-1*H*-pyrrole (**2**) has been synthesized previously and employed in the preparation of the unsymmetrically substituted natural product, verrucarin E.[4] Compound **2** has not, however, found widespread use, nor has it been fully exploited in the preparation of unsymmetrical 3,4-disubstituted pyrroles. The limited use of **2** may be due to the reported difficulties in its synthesis and purification. Muchowski and Naef have published that treatment of 1-[tris(1-methylethyl)silyl]-1*H*-pyrrole (**1**) with two equivalents of N-bromosuccimide (NBS) at -78 °C provides 2,3-dibromo-1-[tris(1-methylethyl)silyl]-1*H*-pyrrole and **2** in a 1:1 ratio. Separation of these two compounds requires careful crystallization at low temperatures.

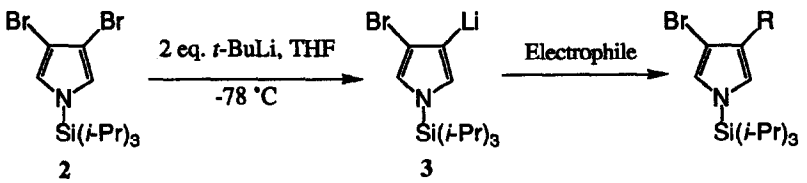
In this Letter we report an improved procedure for obtaining **2** and describe the transformation of this compound to a variety of 3,4-disubstituted pyrroles. Compound **1** was accordingly treated by portionwise addition with 2.1 equivalents of NBS in THF at -78 °C to provide **2** in 78% yield.[5] Both ^1H and ^{13}C NMR spectroscopy failed to show the presence of any 2,3-dibromo-1-[tris(1-methylethyl)silyl]-1*H*-pyrrole. Compound



1 2

2 is isolated as a crystalline solid with melting point 78-80 °C (lit. mp 77 °C). It showed no sign of decomposition when stored at room temperature in the dark for a period of time of up to six months.

When compound 2 is treated with 1 equivalent of *n*-BuLi at -23 °C or 2 equivalents of *t*-BuLi at -78 °C, it undergoes mono-halogen-metal exchange to afford 3-bromo-4-lithio-1-[tris(1-methylethyl)silyl]-1*H*-pyrrole (3). Attempts to generate the dilithiopyrrole with 4 equivalents of *t*-BuLi at -78 °C were not successful, and only products arising from mono-halogen-metal exchange were isolated. Table I shows the reactivity of compound 3 toward a broad range of electrophiles. Methyl iodide (but not a 2° alkyl halide, entry 2), aldehydes, a ketone (entry 7), a dialkyl carbonate (entry 8), and a 3° amide (entry 9) all react smoothly.[6]



2 3

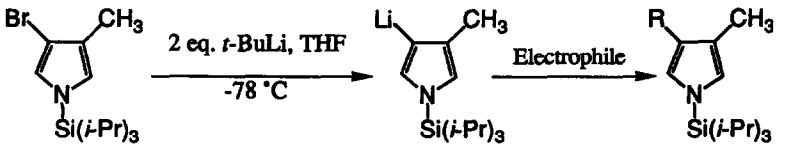
Table I. Reactions of Compound 3 with Various Electrophiles

Entry	Electrophile	R	Isolated Yields
1	CH_3I	CH_3	83%
2	$(CH_3)_2CHI$	N.R.	--
3	$(CH_3)_3SiCl$	$(CH_3)_3Si$	77%
4	$(n\text{-}Bu)_3SnCl$	N.R.	--
5	C_6H_5CHO	$C_6H_5CH(OH)$	82%
6	$C_6H_{13}CHO$	$C_6H_{13}CH(OH)$	78%
7	$(C_6H_5)_2CO$	$(C_6H_5)_2C(OH)$	78% [a]
8	$CH_3OCO_2CH_3$	CO_2CH_3	73% [a]
9	$HCON(CH_3)_2$	CHO	56% [a]

[a] Yields determined after desilylation

As revealed by Table II, symmetrical and unsymmetrical 3,4-di-substituted pyrroles can be synthesized by a second halogen-metal exchange reaction of the first formed mono-bromide. This reaction was tested employing

3-bromo-4-methyl-1-[tris(1-methylethyl)silyl]-1*H*-pyrrole (**4**) as the test substrate and electrophiles similar to those employed in the first stage of the substitution process.



4 **5**

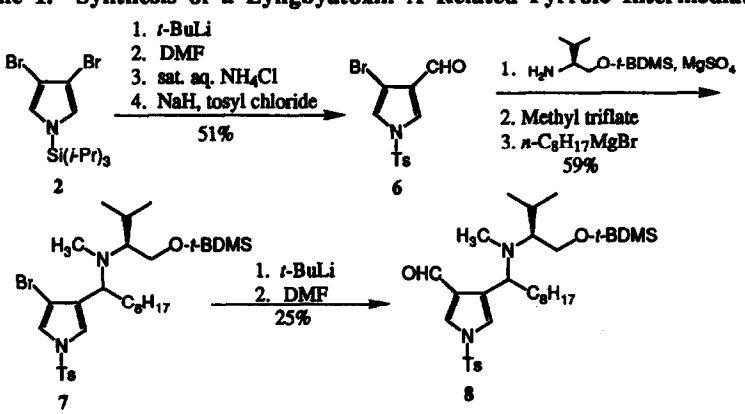
Table II. Reactions of Compound 5 with Various Electrophiles

Entry	Electrophile	R	Isolated Yields
1	CH_3I	CH_3	81%
2	$HCON(CH_3)_2$	CHO	71%
3	$CH_3OCO_2CH_3$	CO_2CH_3	86%
4	C_6H_5CHO	$C_6H_5CH(OH)$	70%
5	$C_6H_{13}CHO$	$C_6H_{13}CH(OH)$	64%
6	$(C_6H_5)_2CO$	$(C_6H_5)_2C(OH)$	48%

[a] Yield determined after desilylation

Following the protocols established in this paper, we have also succeeded in the synthesis of an intermediate for use in the preparation of a lyngbyatoxin A analogue. This chemistry is presented in the accompanying scheme.

Scheme 1. Synthesis of a Lyngbyatoxin A Related Pyrrole Intermediate



In summary we believe that the chemistry reported herein enhances the utility of the dibromide **2** for the preparation of 3,4-disubstituted pyrroles.

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References and Notes

1. For recent reviews, see: (a) Nishizuka, Y. *Nature* **1984**, *308*, 693. (b) Nishizuka, Y. *Nature* **1988**, *334*, 661.
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4. Muchowski, J. M.; Naef, R. *Helv. Chim. Acta* **1984**, *67*, 1168.
5. To a solution of **1** (2.12g, 9.48 mmol) in THF (20 mL) at -78 °C under an Ar atmosphere was added slowly NBS (3.71g, 21 mmol) in THF (30 mL). After addition was completed, the reaction was allowed to warm to room temperature, and concentrated *in vacuo*. Carbon tetrachloride was added, and the solid residue was filtered off. The filtrate was concentrated and chromatographed on silica gel using hexane as eluent to afford 2.83g (78%) of **2** as a colorless solid: mp 78-80 °C; ^{1}H NMR ($CDCl_3$) δ 6.72 (s, 2H), 1.40 (m, 3H), 1.08 (d, J = 7.47 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 11.35, 17.57, 100.88, 123.65; HRMS calcd. for $C_{13}H_{23}Br_2NSi$ (M^+) 378.9966, found 378.9966.
6. All compounds were characterized by IR, ^{1}H and ^{13}C NMR, and HRMS. A typical procedure is as follows: To a solution of **2** (0.5g, 1.31 mmol) in THF (10mL) at -78 °C under an Ar atmosphere was added *t*-BuLi (1.7M in pentane, 1.0 mL, 1.7 mmol). After 30 min, methyl iodide (0.16 mL, 2.62 mmol) was added. After 1 h, the reaction mixture was quenched with saturated sodium bicarbonate and worked up in the usual fashion. The crude product was chromatographed on silica gel using hexane as eluent to afford 0.41g (83%) of **4** as a colorless solid: mp 60-62 °C; ^{1}H NMR ($CDCl_3$) δ 6.70 (d, J = 2.22 Hz, 1H), 6.51 (d, J = 2.22 Hz, 1H), 2.06 (s, 3H), 1.41 (m, 3H), 1.10 (d, J = 7.41 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 10.84, 11.50, 17.74, 100.82, 120.35, 121.53, 122.95; HRMS calcd. for $C_{14}H_{26}BrNSi$ (M^+) 315.1018, found 315.1018.
7. The second halogen-metal exchange reaction was carried out in the same way as described in note 6. Spectroscopic data for the product of entry 1, Table II follow: ^{1}H NMR ($CDCl_3$) δ 6.54 (s, 2H), 2.10 (s, 6H), 1.46 (m, 3H), 1.16 (d, J = 7.47 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 10.26, 11.67, 17.93, 120.22, 121.65; HRMS calcd for $C_{15}H_{29}NSi$ (M^+) 251.2069, found 251.2069.

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