131. 3-Lithiopyrroles by Halogen-Metal Interchange of 3-Bromo-1-(triisopropylsilyl)pyrroles. Synthesis of Verrucarin E and Other 3-Substituted Pyrroles[1])

Preliminary Communication

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Summary

3-Lithio-1-(trimethylsilyl)pyrrole (**7**, *Scheme 2*), obtained by halogen-metal interchange from the 3-bromo compound **2**, reacted with various electrophilic reagents to provide products, which on fluoride ion desilylation, gave 3-substituted pyrroles in good overall yields. One such pyrrole **13** *(Scheme 3)*, was converted into 2-formyl-3-octadecylpyrrole (**14**), reputed to be a metabolite of the marine sponge *Oscarella lobularis*.

3,4-Dibromo-1-(triisopropylsilyl)pyrrole (**5**) was efficiently transformed, by a process involving two consecutive bromine-lithium exchange reactions *(Scheme 4)*, into the antibiotic verrucarin E **17**.

3-Substituted pyrroles have been synthesized by several processes, of variable efficiency which include acid-induced isomerization of the easily accessible α-isomers [1], β-substitution of *N*-(benzenesulfonyl)pyrrole with some electrophiles [2], and the electrophilic substitution of pyrroles bearing a removable deactivating 2-substituent [3] or a sterically demanding *N*-substituent [4] [5]. With regard to the last mentioned process, it was recently [5] shown that *N*-(triisopropylsilyl)pyrrole **1** undergoes highly selective kinetic electrophilic substitution at C(3) and that the silyl moiety is readily removed from the products obtained thereby with tetrabutylammonium fluoride [5] [6][3]). Among the examples reported was the reaction with *N*-bromosuccinimide which gave 3-

[1]) Contribution No. 667 from the Syntex Institute of Organic Chemistry.

[2]) Syntex Research Post-Doctoral Fellow, 1983–1984.

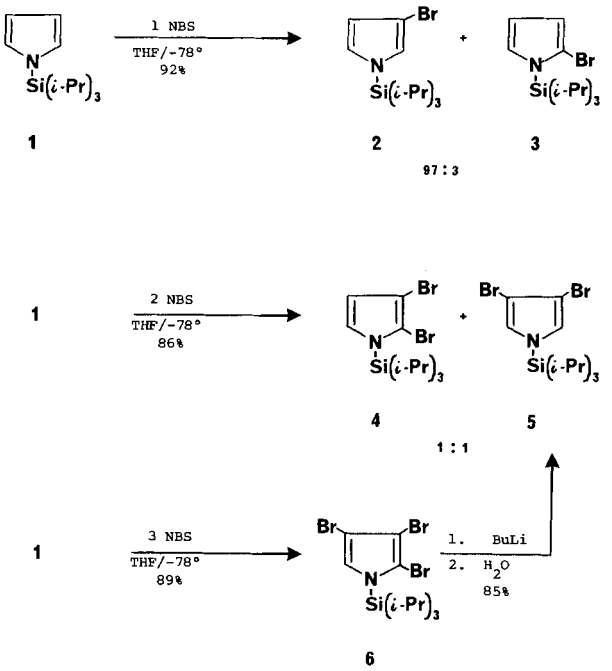
[3]) The 'strong steric screening' properties of the triisopropylsilyl group were first described in [6]. In [5], no acknowledgement of this important observation was made nor was due credit given for the development of the tetrabutylammonium fluoride scission of trialkylsilyl protecting groups [7]. We apologize to Prof. *Corey* and co-workers for this oversight. For other instances where the steric properties of this protecting group have profoundly affected the positional selectivity of a reaction, see [8].

bromo-1-(triisopropylsilyl)pyrrole **2** as the principal product (85:15 of *β- vs.* α-substitution at −80° to −20°). This particular result was of obvious importance because it was expected that **2** itself could serve as the source of a wide variety of 3-substituted pyrroles *via* the corresponding lithio compound. The results described herein confirm this expectation and demonstrate that di- and tribrominated derivatives of *N*-(triisopropylsilyl)pyrrole (**1**) also have a certain degree of synthetic utility.

Bromination of **1** with 1, 2, or 3 molar equiv. of *N*-bromosuccinimide at −78° in THF [9], gave a 97:3 mixture of **2** and the α-bromo isomer **3**, a 1:1 mixture of the 2,3- and 3,4-dibromopyrroles **4** and **5**, or the tribromopyrrole **6** (m.p. 46°) exclusively *(Scheme 1)*[4]). The 3,4-dibromo compound **5**, a solid (m.p. 77°), was easily separated from **4**, an oil, by low-temperature crystallization from pentane. Furthermore, the tribromopyrrole **6** was convertible, in high yield (see *below*) into **5**, thus making the latter compound readily accessible.

The formation of a substantial proportion of **4** in the above mixture is doubly noteworthy. Firstly, it demonstrates that the steric effect of the triisopropylsilyl moiety is not sufficient to entirely overcome the electronic directing effect (to C(2) [10]) of a bromo group at C(3). Secondly, it contrasts with the reported [4c] predominant formation of the 3,4-dibromo compound from *N*-tritylpyrrole and bromine.

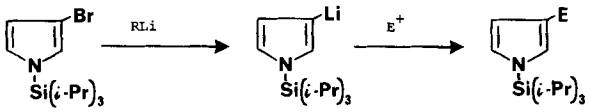
Scheme 1



[4]) All new compounds were characterized by IR, ^{1}H-NMR and mass spectra and had satisfactory elemental analyses.

The lithiation of 3-bromo-1-(triisopropylsilyl)pyrrole (**2**) was effected[5]) by halogen-metal interchange with 1 equiv. of BuLi or 2 equiv. of *t*-BuLi in THF at −78° (0.5 h, *Scheme 2*). The 3-lithiopyrrole derivative **7** reacted with a broad spectrum of electrophilic reagents (see *Table*) which included alkyl halides (benzyl bromide gave bibenzyl, secondary alkyl halides were dehydrohalogenated), aldehydes, cyclohexanone, DMF, carbon dioxide, *etc.*, and in some instances, the products thus obtained were desilylated with tetrabutylammonium fluoride (THF, room temp., 5 min) to the 3-substituted pyrroles **9**. Therefore **7** is an effective, formal equivalent of 3-lithiopyrrole.

Table. *3-Substituted Pyrroles from 3-Lithio-1-(triisopropylsilyl)pyrrole*



RLi (equiv.)	Electrophile	E in product	Yield [%]	M.p. [°C]
t-BuLi (2)	CH_3I	CH_3	92	oil
t-BuLi (2)	$C_{18}H_{37}I$	$C_{18}H_{37}$	88	glass
t-BuLi (2)	$(CH_3)_3SiCl$	$(CH_3)_3Si$	87	oil
BuLi (1)	CO_2	COOH[a])	88	162
t-BuLi (2)	HCHO gas	CH_2OH	73	37
BuLi (1)	C_6H_5CHO	$CHOHC_6H_5$	48	132
t-BuLi (2)	Cyclohexanone	[b])	69	oil
BuLi (1)	DMF	CHO[c])	82	oil
t-BuLi (2)	$CH_3CONCH_3OCH_3$	$COCH_3$[d])	61	69

[a]) Desilylated (88%) to pyrrole-3-carboxylic acid, m.p. 149° ([19]: m.p. 150–150.5°).
[b]) Dehydration effected by heating crude product at 150° for 45 min.
[c]) Desilylated (86%) to pyrrole-3-carbaldehyde, m.p. 63° ([20]: m.p. 63–63.5°).
[d]) Desilylated (84%) to 3-acetylpyrrole, m.p. 111–112° ([20]: m.p. 114–115°).

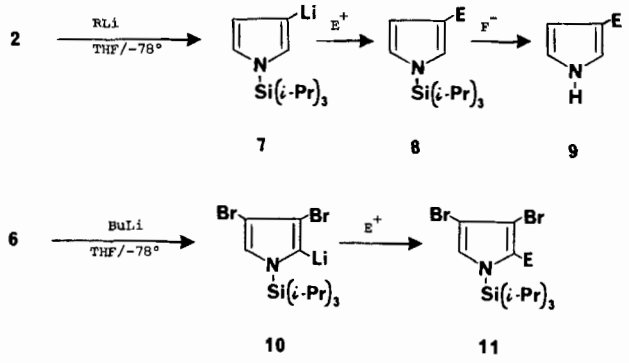
The mono-lithiation of the 3,4-dibromo and 2,3,4-tribromo compounds **5** and **6** was accomplished under conditions analogous to those used for the formation of **7**. The α-lithiated species **10** *(Scheme 2)*, which reacted with the usual range of electrophiles[6]), was formed essentially exclusively (> 99%) as deduced by protonolysis to 3,4-dibromo-1-(triisopropylsilyl)pyrrole (**5**) (85% yield).

The methodology described above was then utilized to synthesize a purported metabolite **14** of the marine sponge *Oscarella lobularis* [14] as well as the antibiotic verrucarin E (**17**) [15]. Thus, for the former substance, 3-octadecyl-1-(triisopropylsilyl)pyrrole (**12**) *(Scheme 3)*, obtained in nearly 90% yield from the lithio compound **7** and octadecyl iodide, was desilylated (76%) and the 3-substituted pyrrole **13** (m.p. 53°), obtained in this way, was formylated under *Vilsmeier-Haack* [16] conditions. A

[5]) *N*-Benzyl-3-lithiopyrrole has been obtained from the bromo compound and metallic lithium [11] and 4,4-dimethyl-2-(*N*-methylpyrrol-2-yl)oxazoline can be selectively lithiated at C(3) [12]. The usefulness of these reagents is minimal because removal of the *N*-substituent is not possible. *N*-(Trimethylsilyl)pyrrole is metallated to a considerable extent at C(3) with excess *t*-BuLi in pentane [13].

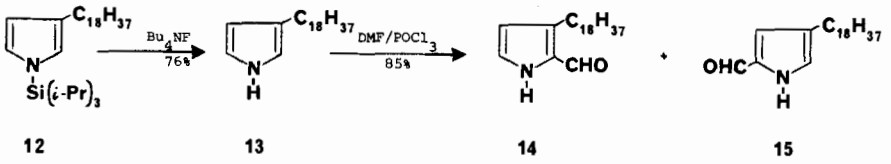
[6]) A detailed description of this study will be reported in the full paper.

Scheme 2



crystalline (m.p. 72–75°) 3:1 mixture (as yet not separable) of the supposed natural product **14** and the isomeric aldehyde **15** was isolated in 85% yield[7]). To synthesize verrucarin E (**17**), the 3,4-dibromo compound **5** reacted sequentially, in one pot *(Scheme 4)*, with BuLi (1 equiv., THF/–78°), *N*-methoxy-*N*-methylacetamide [17], *t*-BuLi (2 equiv., THF/–78°) and dry, gaseous formaldehyde, to produce the 3-acetyl-4-hydroxymethylpyrrole derivative **16** (m.p. 91°) in 58% overall yield, after chromatographic purification on silica gel. Desilylation of **16** gave crystalline verrucarin E (**17**), m.p. 90° ([15a]: m.p. 90.5–91°), the NMR spectral characteristic of which were identical to those published [15a]. This synthesis of **17** is considerably more efficient (44% yield overall) than two of those previously reported [15] [18] and compares not too unfavorably with the elegant and efficient three-step synthesis of *Gossauer & Suhl* [21].

Scheme 3



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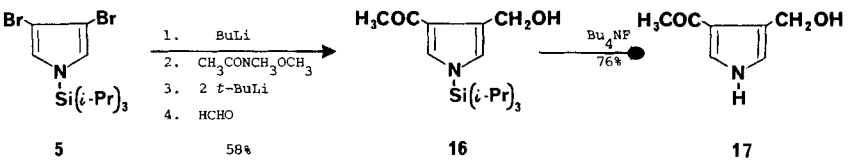
7) **14**: ^{1}H-NMR (300 MHz, CCl_4): 0.88 (*t*, *J* = 6.5, 3 H, CH_3CH_2); 1.25 (*m*, 30 H); 1.63 (*m*, 2 H, CH_2); 2.75 (*m*, *J* = 7.6, 2 H, CCH_2); 6.05 (*d*, *J* = 2.5, 1 H, H–C(4)); 7.03 (*dd*, *J*(4,5) = 2.5, *J*(5,CHO) = 1.1, 1 H, H–C(5)); 9.61 (*d*, *J* = 1.1, 1 H, CHO); 10.95 (br. *s*, 1 H, NH). The ^{1}H-NMR spectrum of **14** is similar to but not identical with that reported in [14a] [0.9 (*t*, *J* = 6, 3 H); 1.26 (*m*, 2 H); 2.70 (*t*, *J* = 6, 2 H); 5.94 (*d*, *J* = 2.4, 1 H); 6.76 (*d*, *J* = 2.4, 1 H); 9.22 (*s*, 1 H); 11.0 (br. *s*, 1 H, NH)]. The latter parameters are, however, nearly identical with those in [14b] for the 2,5-disubstituted isomer, except that these authors observed a larger coupling constant (*J* = 3.7) for the ring protons and two-proton *m* at 1.68.

Scheme 4



5 58% **16** **17**

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