Lithiations of 1-Trialkylsilylpyrroles : N to C Silyl Group Rearrangement

By **Derek J. Chadwick** * and **Simon T. Hodgson,** The Robert Robinson Laboratories, Department of Organic Chemistry, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

The sites of metallation with alkyl-lithium reagents of 1-trimethylsilyl- and 1-triethylsilyl-pyrroles have been explored under a variety of conditions. With short reaction times, Bu^nLi reacts with 1-trimethylsilylpyrrole in hexane predominantly at the 2-position though with Bu^tLi in pentane the unusual 3-metallated product is preferred. During prolonged reaction of 1-trimethylsilyl- and 1-triethylsilyl-pyrroles with Bu^tLi, the 2-monolithio- and the 2,4- and 2,5-dilithio-intermediates are formed, in which, unexpectedly, the silyl groups migrate to the pyrrole 2-position. Under conditions favouring enhanced ionicity, Bu^nLi cleaves the $N-SiMe_3$ bond in preference to ring metallation.

PREVIOUSLY we have reported [1,2] that during the metallation of 1-methylpyrrole with Bu^nLi, mixtures of 2-monolithio-, 2,5-dilithio- and (the unusual) 2,4-dilithio-pyrroles are formed and, under thermodynamic control of the reaction, the 2,4-isomer may be formed exclusively. In a more comprehensive metallation study [3] we have explored the effects of change of 1-alkyl pyrrole substituent, of addition of complexing agents, and of variation in the alkyl-lithium agent.

In a continuation of our metallation studies, lithiations of pyrroles bearing a 1-trialkylsilyl substituent have been examined in order to explore the possibility that a trialkylsilyl substituent might exhibit a β-metallating (directing) effect, but be removable (after quenching of the lithio-intermediates with a suitable electrophile), thus providing a synthetical route to 2,4- and 3-substituted 1-*H*-pyrroles, which are not easily prepared with traditional methodology. To this end, 1-trimethylsilyl-pyrrole (1) [4a-c] and 1-triethylsilylpyrrole (2) [4a] were synthesised *via* silylation of pyrrolyl-lithium (prepared from pyrrole and Bu^nLi) with the appropriate trialkyl-chlorosilane and subjected to a variety of metallation conditions; the mixtures of lithio-intermediates were quenched with (*a*) carbon dioxide and subsequently converted into methyl esters with diazomethane, (*b*) deuterium oxide, and (*c*) water, and analysed by n.m.r. spectroscopy in order to deduce the product distributions. In several cases, absolute yields were checked by work-up procedure (*a*) followed by t.l.c. separation of the components: results of these studies demonstrated that all consumed starting material was accounted for by the identified products.

RESULTS AND DISCUSSION

The metallation experiments are divided into four series and are presented and discussed under separate headings. Where reaction numbers are quoted, these are the same as those used in the Experimental section for a particular pyrrole substrate.

(*A*) '*Short*' *Metallations of* 1-*Trimethylsilylpyrrole: Carbon Dioxide Quench and Subsequent Methylation.*—1-Trimethylsilylpyrrole (1) was metallated with Bu^nLi and Bu^tLi under a variety of conditions with relatively short reaction times and the lithio-intermediates were con-

verted into mixtures of methyl esters in which four compounds were detected: the 1-ester (3), 2-ester, (4) 3-ester (5), and 2,5-diester (6) (Scheme 1). The instability of 1-trimethylsilylpyrrole towards acid- and base-catalysed hydrolysis has been previously reported: [4b] since such
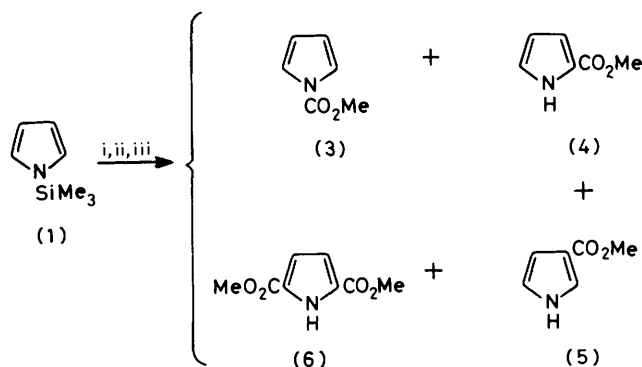
SCHEME 1

Reagents: i, Bu^nLi–hexane or Bu^tLi–pentane; ii, CO_2, Et_2O then HCl; iii, CH_2N_2, Et_2O

conditions occur in the work-up procedures used here, esters containing a 1-trimethylsilyl substituent were not detected. A summary of the product distributions and overall reaction yields is given in Table 1. The overall yields were calculated *via* recovery of unchanged starting material and the assumption (justified above) that the balance of starting material had been transformed completely into the identified products: such yields are necessarily approximate.

Several conclusions may be drawn from the results presented in Table 1. With Bu^nLi in hexane: (*a*) the 2-ester predominates always [reactions (i) to (iv)]; (*b*) formation of the 2,5-diester and the 3-ester is favoured as the reaction time is extended [reactions (ii) and (iii)] and when the amount of Bu^nLi relative to substrate is increased [reaction (iv)]; (*c*) the 1-ester is formed exclusively when either the complexing agent TMEDA (*N*,*N*,*N'*,*N'*-tetramethylethylenediamine) is added [reactions (vi) and (viii)] or when the hexane solvent is replaced by ether [reaction (v)] (the attack of the metallating agent at silicon in preference to proton abstraction, to give the 1-ester, may be rationalised by a consideration of the structure of Bu^nLi: in hydrocarbon solvents,

viz. hexane, Bu^{n}Li is hexameric [5] and so is a relatively hindered nucleophile; Bu^{n}Li, however, forms 1 : 1 complexes with TMEDA and ether and, therefore, its nucleophilicity probably increases under these conditions); (d) change of metallating agent to Bu^{t}Li [reactions (viii) and (ix)] has a pronounced effect on the product distributions [compared with reaction (i)]; although small amounts of the 1-ester and 2,5-diesters are observed, the 3-ester is the most abundant product,

(C) 'Long' Metallations of 1-Triethylsilyl- and 1-Trimethylsilyl-pyrroles: D$_2$O and H$_2$O Quench.—In a further experiment, 1-triethylsilylpyrrole (2) was boiled with a large excess of Bu^{t}Li in pentane and aliquots from the reaction mixture were taken after 1 d and 3 d and quenched with either water or deuterium oxide affording 2-triethylsilylpyrrole (11) and deuterio-2-triethylsilyl-pyrroles [(12) and (13)] respectively (Scheme 4). Based on the amount of starting material present in the mix-

TABLE 1

Experimental conditions and results of 'short' metallations of (1)

Reaction no.	Bu^{n}Li[a] : substrate	°C	t/h	Product ratios				Overall yield (%)
				(3)[g]	(4)	(5)	(6)	
(i)	1 : 1	R[b]	3	—	Only	—	—	50
(ii)	1 : 1	R	6	1	9	—	1.75	56
(iii)	1 : 1	R	8	1	8	1	1.5	55
(iv)	4.5 : 1[c]	R	3	1	5	1	2.5	45
(v)	1 : 1[c]	R	3	Only	—	—	—	40
(vi)	2.5 : 1[d]	25	0.5	Only	—	—	—	49
(vii)	4.5 : 1[d]	−50	0.5	Only	—	—	—	10
	Bu^{t}Li[e] : substrate							
(viii)	1 : 1	R	3	All products present				50[f]
(ix)	2.5 : 1	R	3	1	1	3.3	1	51

[a] Hexane solvent. [b] R = Reflux. [c] Et$_2$O solvent. [d] N,N,N',N'-Tetramethylethylenediamine (equimolar with respect to Bu^{n}Li) was added. [e] Pentane solvent. [f] Product ratios were not determined; in addition, a small amount of 1,3-bismethoxy-carbonylpyrrole was isolated. [g] Products were identified by comparison of physical data with those of authentic specimens previously prepared by unambiguous routes and with those from the literature (references are given in the Experimental section), and by analysis of the highly diagnostic ring proton chemical-shifts and coupling constants.

whilst the amount of the 2-ester is relatively decreased.

The emergence of the 3-mono-ester may be a reflection of the greater basicity of the t-butyl carbanion over the n-butyl analogue, or of the different oligomeric structures of the two organolithium compounds (Bu^{t}Li is tetrameric in hydrocarbon solvents [5]) or simply of the increased hindrance experienced by the t-butyl carbanion (or of a combination of these factors).

(B) 'Long' Metallations of 1-Triethylsilylpyrrole: Carbon Dioxide Quench and subsequent Methylation.— When 1-triethylsilylpyrrole (2) was boiled with one equivalent of Bu^{n}Li in hexane or an excess of Bu^{t}Li in pentane for 3 h, no metallation was observed. Compared with the trimethylsilyl group, the triethylsilyl group presumably exerts a greater hindering effect on the metallating agents. The boiling, however, of 1-triethyl-silylpyrrole with a large (4 molar) excess of Bu^{t}Li for 3 d (and subsequent carboxylation and methylation) gave rise to some unexpected products in which rearrangement of the triethylsilyl group to the 2-position has occurred in conjunction with metallation of the ring (Scheme 2). The silyl methyl esters (7), (8), and (9) were obtained as a mixture in a ratio 4 : 1.5 : 1 respectively. Chromatography afforded the pure compounds whose structures were determined from n.m.r. coupling-constant and chemical-shift measurements. A further proof of structure, however, was available because the 2-triethylsilyl group is cleaved by trifluoroacetic acid at room temperature yielding the simple esters (5) and (4) (whose n.m.r. spectra are known) and (10) (whose n.m.r. spectrum is very similar to the known 1-t-butyl-derivative [3]) (Scheme 3).
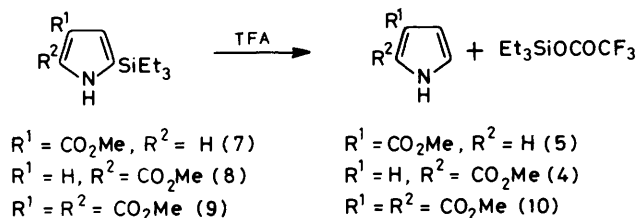
tures, the conversion into the protio-product was 90% after 3 d and into the deuterio-products was 62% after 1 d and 91% after 3 d.

The fortuitous discovery of the rearrangement process during the metallation of 1-triethylsilylpyrrole prompted a reappraisal of the metallation of 1-trimethylsilylpyrrole: after the boiling of 1-trimethylsilylpyrrole with a large
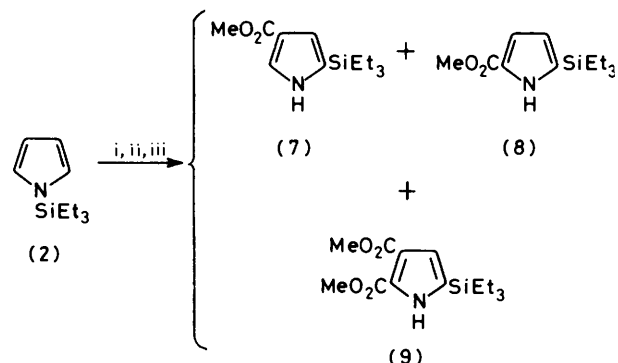

SCHEME 2   Reagents: i, Bu^{t}Li–pentane; ii, CO$_2$ then HCl; iii, CH$_2$N$_2$

excess of Bu^{t}Li in pentane for 3 d the mixture was quenched with either water or deuterium oxide. Owing to the absence of starting material the reaction was presumed to proceed with approximately 100% conversion into products. From the water quench the rearranged 2-trimethylsilylpyrrole and pyrrole were detected in a 5 : 2 ratio and from the deuterium oxide quench 2-trimethylsilylpyrrole (deuteriated in the 1-, 4-, and 5-positions) and pyrrole (deuteriated in the 2- and 5-positions) were detected in an approximate ratio of 4 : 3.

SCHEME 3

$R^1 = CO_2Me$, $R^2 = H$ (7) $R^1 = CO_2Me$, $R^2 = H$ (5)
$R^1 = H$, $R^2 = CO_2Me$ (8) $R^1 = H$, $R^2 = CO_2Me$ (4)
$R^1 = R^2 = CO_2Me$ (9) $R^1 = R^2 = CO_2Me$ (10)

(The trimethylsilyl-cleaved pyrroles presumably arise from the hydrolysis of 1-trimethylsilylpyrroles during the work-up procedure.)   The above deuteriation experiments are summarised in Table 2: the presence of a 4,5-dideuterio-isomer (strictly 1,4,5-trideuterio-isomer) is

(11)

(12)   (13)
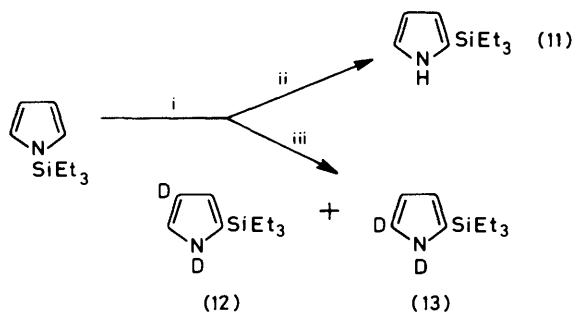
SCHEME 4   *Reagents*: i, Bu^{t}Li, pentane, reflux;
ii, H$_2$O; iii, D$_2$O

presumed to be relatively small [from carboxylation/methylation of 1-triethylsilylpyrrole (Scheme 2)] and should not affect the 2,4-/2,5-ratio, although it will affect the ' % D-incorporation ' values.

(*D*) ' *Short* ' *Metallations of* 1-*Trimethylsilylpyrrole:* D$_2$O *and* H$_2$O *Quench.*—The ' short ' metallation of 1-trimethylsilylpyrrole with Bu^{t}Li under reflux for 3 h

TABLE 2

Results of D$_2$O work-up of ' long ' metallations of (1) and (2)

| Substrate | Reaction time (d) | D-Incorporation (%) [a] | | [2,4-] [b] |
		4-D	5-D	[2,5-]
1-Triethylsilylpyrrole	{ 1	54	39	1.4
	{ 3	48	40	1.2
1-Trimethylsilylpyrrole	3	38	13	3

[a] Percentage deuterium incorporation into the 4- and 5-positions is assessed *via* the measurement of n.m.r. integrals of the 4- and 5-protons relative to the 3-proton in the rearranged product; it is assumed that no metallation has occurred at the 3-position of the 2-trialkylsilylpyrroles.   [b] The 2,4-/2,5-ratio (obtained from 4-D/5-D ratio) represents the ratio of 2,4- and 2,5-dilithio-intermediates from which the deuteriated-2-trialkylsilylpyrroles are formed.

was reinvestigated.   In the belief that any rearranged 2-trialkylsilylpyrroles are less likely to be cleaved under basic conditions than under acidic conditions (*e.g.* during the carboxylation work-up procedure), the anions were quenched with either water or deuterium oxide to give, respectively, a mixture of starting material, 2-trimethylsilylpyrrole and pyrrole in a ratio 6 : 3 : 2, and a mixture

of starting material, 2-trimethylsilylpyrrole and pyrrole (in which little deuteriation of the ring positions was apparent) in a ratio 1 : 1 : 6.   The conclusions from these experiments are two-fold: (*a*) the silyl group rearrangement is relatively slow so that after 3 h at reflux temperature little rearrangement takes place, and (*b*) the degree of metallation of 1-trimethylsilylpyrrole after 3 h may be smaller than perhaps the results presented in Table 1 suggest.

The rearrangement of the triethyl- and trimethyl-silyl groups is unusual in that it occurs from an *N*-centre to a *C*-centre (silyl groups usually migrate from carbon to a more electronegative centre such as oxygen or sulphur [6]). The silyl group probably migrates to an α-carbanion to produce the thermodynamically more stable *N*-anion (Scheme 5).   Support for this argument is provided by
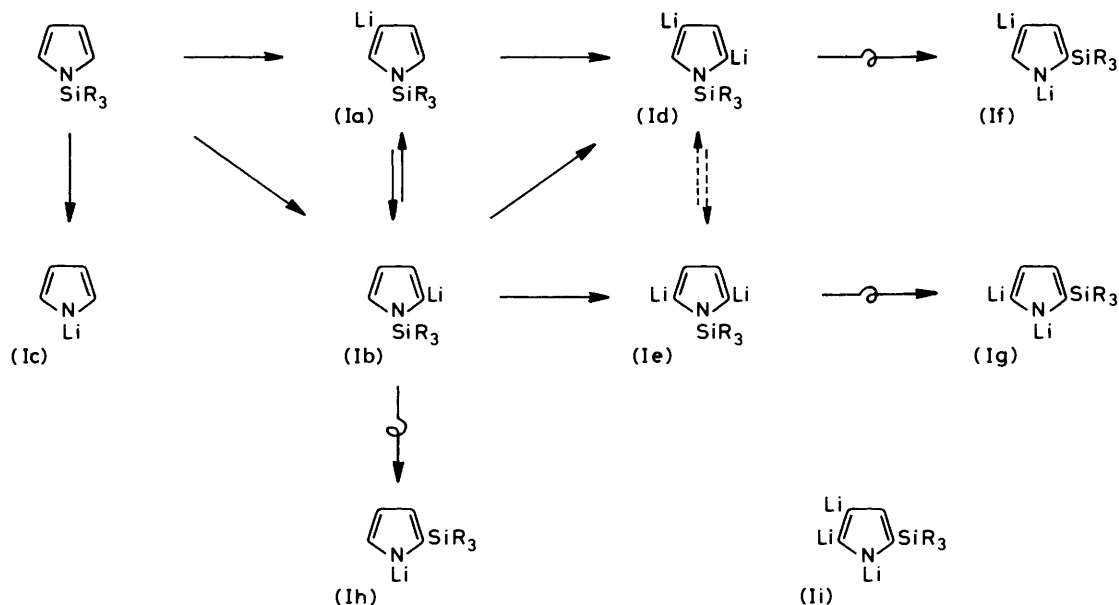
SCHEME 5

the rearrangement of aminomethylsilanes to silylamines [7] (promoted by Bu^{n}Li) in which the N to C migration was found to be reversible so that the equilibrium position was controlled by the relative stabilities of the *N*- and *C*-anions.   In one example, the reaction was actually approached from the opposite side, *i.e.* a silyl group migrated to a *C*-anionic centre to give an *N*-anion (as we propose in the present work).

The reasons why the *N*-anions of the rearranged 2-triethylsilylpyrroles apparently do not react with CO$_2$ to form (after methylation) the *N*-methoxy-carbonyl-derivatives (Scheme 2) may be two-fold: steric hindrance in the anions may be sufficient to disfavour nucleophilic attack on CO$_2$ or (more likely) the *N*-carboxylic acids are formed (*i.e.* nucleophilic attack does occur), but subsequently undergo decarboxylation.

A reaction scheme is tentatively proposed for the metallation–rearrangement process during the reaction of 1-trimethylsilyl- and 1-triethylsilyl-pyrroles with Bu^{t}Li (Scheme 6; the intermediates are labelled I).   Some of the steps represented as being irreversible are potentially reversible although the data are at present insufficient to allow clarification on this point.

The product distribution from the reaction (ix) (Table 1) suggests that the 3-lithio-intermediate (Ia) is formed faster than the 2-lithio-intermediate (Ib).   Another competing process is cleavage of the silyl group leading to (Ic): it is assumed that once an *N*-lithiopyrrole is formed then further metallation is inhibited (pyrrole itself reacts with excess of Bu^{n}Li to form essentially only the *N*-lithio-derivative [2]).   As the reaction proceeds the 3-isomer (Ia) may undergo further metallation to give the 2,4-isomer (Id) which subsequently rearranges to (If).   Alternatively, the 3-isomer (Ia) may exchange with another pyrrole species to give the 2-litho-intermediate (Ib) which may undergo further metallation to

SCHEME 6

give the 2,5-isomer (Ie) [or the 2,4-isomer (Id)] with subsequent rearrangement to (Ig) [or (If)]. Alternatively, (Ib) may rearrange to (Ih) before further metallation. Differences in the product distributions between 1-trimethylsilyl- and 1-triethylsilyl-pyrrole may be attributed to differences in the preferred pathways: in the case of 1-trimethylsilylpyrrole the 2,4-/2,5-ratio is *greater* and the degree of dimetallation (particularly 2,5-) indicated by the % D-incorporations (Table 2) is *less* when compared with 1-triethylsilylpyrrole. Moreover, the trimethylsilylpyrrole product unaccounted for (*ca.* 50%) in Table 2 which is undeuteriated but rearranged must be (Ih). These observations suggest that when compared with the triethylsilylpyrroles, the trimethylsilylpyrrole (Ib) rearranges to (Ih) faster than metallation to the 2,5-isomer (Ie). This pathway preference for the trimethylsilylpyrroles might conceivably explain the relatively large 2,4-/2,5-isomer ratio.

The small decrease in the 2,4-/2,5-ratio for triethylsilylpyrroles with time may suggest some equilibration between the 2,4- and 2,5-isomers (Id) and (Ie). The trisanion (Ii) presumably arises from the dilithio-intermediates (Id) and (Ie). The silicon-cleaved intermediate (Ic) only appears from attack of the metallating agent at the relatively unhindered trimethylsilyl group.

In conclusion, it is useful to compare the results of the present study with those of our previous work on *N*-alkylpyrroles. Three striking differences have emerged in the work on *N*-silylated pyrroles: (*a*) the isolation of the 3-monosubstituted ester (5); (*b*) the N to C trialkylsilyl group rearrangement, and (*c*) N–Si bond cleavage competing efficiently with proton abstraction [(b) and (c) clearly demonstrate the relative weakness of the N–Si bond].

EXPERIMENTAL

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