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Aryl N- and O-Trimethylsilyl Substituents: Reactivity Toward Organolithium Compounds*

Isamu Arai, Kyong-Hwi Park, and G. Doyle Daves, Jr.
Department of Chemistry
Oregon Graduate Center
Beaverton, Oregon 97005

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Summary

The efficacy of using the trimethylsilyl group for protection of aryl amino and hydroxy substituents during reactions involving organolithium reagents has been assessed. Bromotrimethylsiloxy-benzenes or -pyrimidines reacted with n-butyl lithium by initial metal-halogen exchange followed by intra- or intermolecular rearrangement of trimethylsilyl from oxygen to the carbanionic center. Trimethylsilyl groups on aryl nitrogen are stable to conditions of organolithium coupling reactions. It is suggested that for aryl O- and aryl N-trimethylsilanes, the observed differences in reactivity at silicon are owing to the marked differences in basicity of the respective leaving groups ($PhOH \rightleftharpoons PhO^-$, $pK_A \sim 10$, $PhNH_2 \rightleftharpoons PhNH^-$, $pK_A \sim 25$).

Introduction

The use of trimethylsilyl groups for protection of substituents on aromatic rings during organometallic coupling reactions is attractive because (a) trimethylsilyl groups are readily introduced and removed and (b) they confer high solubility in aprotic solvents for otherwise quite

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*For a preliminary report of a portion of this work, see ref. 1.

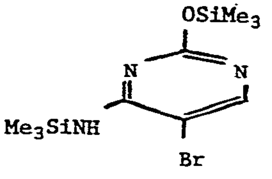
insoluble polar compounds. Because the available literature is inconclusive, we have carried out a limited study of the efficacy of using the trimethylsilyl group for protection of aryl amino and hydroxy substituents during reactions involving organolithium species.

Of particular interest to us were organometallic reactions of trimethylsilylated pyrimidines. Two pertinent reports are available. David and Lubineau [2] have successfully used, as a reactive intermediate, the lithium derivative prepared by treatment of 5-bromo-2,4-bis N,O-trimethylsilylcytosine(I) with two equivalents of n-butyl lithium. However, Pichat and coworkers[3] prepared the corresponding lithium derivative from 2,4-bis O-trimethylsilyl-uracil(II) [4] and, to their surprise, found it "passive" in the presence of methyl iodide. We have confirmed and explained these seemingly conflicting results [1] and have extended them by study of the lithium derivative prepared from 5-bromo-2,4-bis N,O-trimethylsilylisocytosine (III). In addition we have generated aryl lithium species derived from a number of trimethylsilylated phenols and anilines and assessed their stabilities.

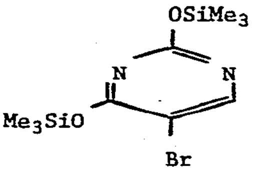
Results

5-Bromo-2,4-bis N,O-trimethylsilylcytosine (I) [2], upon treatment with two equivalents of n-butyl lithium, yields a dilithium derivative which is stable; after one hour at room temperature protonation and hydrolysis of the trimethylsilyl groups yields cytosine essentially quantitatively. However, similar treatment of either II or III produces different results. In both cases migration of a trimethylsilyl group to carbon occurs yielding, after hydrolysis, 5-trimethylsilyluracil (IV) [1] and 2-amino-5-trimethylsilyl-4-pyrimidinone (5-trimethylsilylisocytosine, V) respectively. These data are summarized in Table 1. While the formation of C-trimethylsilyl compounds IV or V is temperature dependent (Table 1), even at -100° rearrangement of the trimethylsilyl group to carbon was not eliminated and formation of appreciable yields of IV and V was still observed.

To assess the lability of the 5-pyrimidinyl C-Si bond under hydrolytic conditions, 5-trimethylsilyluracil (IV) was heated in methanol-6N hydrochloric acid under reflux. A reaction time of three hours was required for complete hydrolysis of IV to uracil.



I



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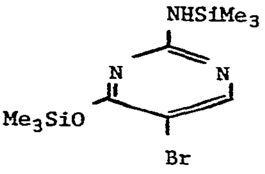

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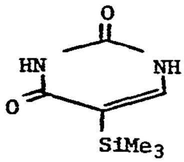
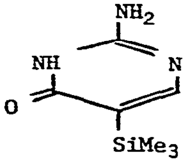


IV



V

Table 2 contains results obtained when the three isomeric bromo phenoxytrimethylsilanes [5] were treated with n-butyl lithium and the resulting reaction mixtures were analyzed following acidification; in each case the predominant reaction was rearrangement of trimethylsilyl from oxygen to carbon. In contrast, no rearrangement occurred when o-bromophenylaminotrimethylsilane was treated with n-butyl lithium (eq. 1) in accord with the results obtained with the pyrimidine analog, III [1,2]. Finally, treatment of an equimolar mixture of bromobenzene and phenoxytrimethylsilane [6] with n-butyl lithium produced phenyltrimethylsilane [7] (eq. 2) establishing unambiguously the intermolecular nature of the trimethylsilyl transfer in this instance.

Table 1

Reactions of Trimethylsilylated 5-Bromopyrimidines (I-III) with n-Butyl Lithium in Tetrahydrofuran

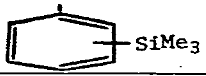
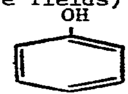
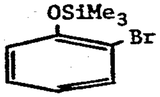
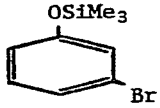
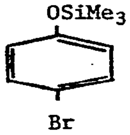
Starting Material	Equivalents n-Butyl Lithium	Reaction Temperature (°C)[a]	Hydrolysis Product[b] (Yield)	Rearrangement Products[b] (Yield)
5-Bromo-2,4-bis N,O-trimethylsilylcytosine (I)	2	25	cytosine (94%)	not detected
5-Bromo-2,4-bis O-trimethylsilyluracil (II)	1	25	uracil (26%)	5-trimethylsilyluracil, IV (73%)
	1	-78	uracil (34%)	5-trimethylsilyluracil, IV (63%)
	1	-100	uracil (61%)	5-trimethylsilyluracil, IV (30%)
5-Bromo-2,4-bis-N,O-trimethylsilylisocytosine (III)	2	25	isocytosine (23%)	5-trimethylsilylisocytosine, V (57%)
	2	-78	isocytosine (64%)	5-trimethylsilylisocytosine, V (17%)
	2	-100	isocytosine (76%)	5-trimethylsilylisocytosine, V (11%)

[a] In all cases *n*-butyl lithium was added to a solution of 10 mmol of the bromopyrimidine in 100 ml of tetrahydrofuran at -78° (-100°) with stirring. Following completion of *n*-butyl lithium addition (15 min.), reaction mixtures were either maintained one hour at -78° (-100°) or warmed to 25° and maintained for 45 minutes.

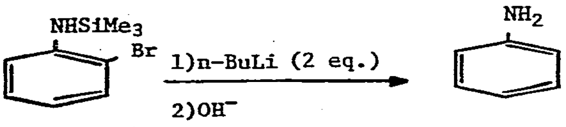
[b] Reactions were terminated by addition of methanol. N- and O-trimethylsilyl groups were removed by hydrolysis with dilute hydrochloric acid prior to product isolation.

Table 2

Reactions of Ortho-, Meta- and Para-Bromo Phenoxytrimethylsilanes with n-Butyl Lithium in Tetrahydrofuran at -78° for 3 Hours

	Products (Relative Yields)[a]	
		
	-100	trace
	87	13
	83	17

[a] Obtained by gas chromatographic analysis (2m x 2 mm glass column packed with 1.5% OV 101 on W-HP, temperature programmed at 10°/min. from 50° to 250°) following acid hydrolysis of trimethylsiloxy groups.

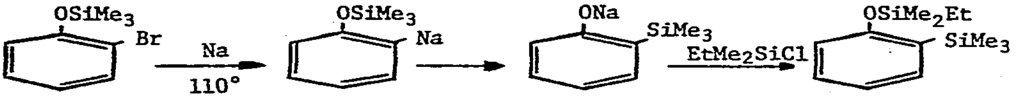


(1)

(2)

Discussion

In what appears to be the earliest relevant study, Speier[6] investigated the reactions of o- and p-chlorophenoxytrimethylsilanes with molten sodium in refluxing toluene in the presence of ethyldimethylchlorosilane. Using the ortho compound, he isolated only the rearranged produce o-trimethylsilylphenoxyethyldimethylsilane and postulated the reaction sequence:



(3)

Using the para isomer, Speier [6] isolated a mixture of products resulting from both silylation of the initially formed arylsodium compound and from rearrangement of the trimethylsilyl group from oxygen to carbon. Following this initial study Frisch and Shroff [8], Neville [9] and Cooper [10] successfully used m- and p-halophenoxytrialkyl(aryl)silanes in Wurtz-Fittig, Grignard and organolithium coupling reactions.

In similar studies, Bassindale and Walton [11] and Bailey and Taylor [12] established that o- or p-bromophenylthiotrimethylsilanes, upon treatment with n-butyl lithium, yielded, by migration of trimethylsilyl from sulfur to carbon, the respective o- and p-thiophenyltrimethylsilanes. In the case of the para isomer, generation of the sodium derivative in the presence of bromotriethylsilane allowed the initially formed organometallic compound to be trapped before rearrangement occurred [11]. Walton [13] and Broser and Harrer [14] have shown that m- and p-halo-(N,N-bis-trimethylsilyl)anilines undergo organometallic coupling reactions without rearrangement. Recently, trimethylsilyl groups have been used for protection of amino and hydroxy substituents in Ullmann and related organocopper coupling reactions [15].

Our results and those of earlier studies (see above) establish that the trimethylsilyl group is effective for protection of amino substituents on aromatic rings during reactions involving organometallic reagents. Interestingly, amino substituents are masked equally well using a single trimethylsilyl group (compound I and o-bromophenylaminotrimethylsilane, eq. 1) as with two (m- and p-halo-N,N-bis-trimethylsilylanilines [13,14]). Equally clearly, the studies of Bassindale and Walton [11] and Bailey and Taylor [12] establish that trimethylsilylthioethers are labile in the presence of organometallic species. The situation with respect to phenoxytrimethylsilanes is more complex. Several reports [6-10,15] of the successful use of trimethylsilyl groups to protect phenolic oxygens are available. However, displacement of trimethylsilyl from oxygen by carbanion reagents is facile under appropriate conditions [1,6,16]. The similarity of results obtained by reaction of phenyl lithium with phenoxytrimethylsilane (eq. 2) with those in which an aryl trimethylsiloxy substituent is meta or para disposed to an aryl carbanion (Table 2) leaves little doubt that these reactions are also intermolecular [6]. However, when these functionalities bear an ortho relationship the migration of silicon from oxygen to carbon is particularly facile [1,3,6] (II, III, Table 1; o-bromophenoxytrimethylsilane, Table 2) suggestive that, in these cases, an intramolecular process occurs [1,6]. This possibility receives support from observations that the intermediate ortho carbanion cannot be trapped even when generated in the presence of excess ethyldimethylchlorosilane [6] (eq. 3) whereas the corresponding carbanion with p-trimethylsilylthio, a much more reactive substituent than trimethylsiloxy, was readily captured using this procedure [11].

From consideration of mechanisms for displacements at silicon advanced by Sommer [16], the observed intermolecular displacements of aryloxy can be characterized as four-center S_Ni-Si reactions. Both the relatively poor leaving group involved ($\text{PhOH} \rightleftharpoons \text{PhO}^-$, $pK_A \sim 10$) [17] and the covalent nature of the aryl lithium bond accord with this designation [16]. Similarly, the failure to observe displacement of trimethylsilyl from nitrogen can be attributed to the extremely poor ArNR^- leaving group ($\text{PhNH}_2 \rightleftharpoons \text{PhNH}^-$, $pK_A \sim 25$) [17]. The observation that 1-[dimethyl-(1',1'-dimethylethyl)silyl]-2-lithioindole undergoes facile rearrangement to produce 2-[dimethyl-(1',1'-dimethylethyl)silyl]indole [18] provides further support for this conclusion since the nitrogen leaving group in this case is much more favorable. As noted earlier [1], the best analogy for the ortho rearrangements appears to be the similar anionic shifts of silicon from oxygen to carbon in aliphatic systems studied by Wright and West [19]*.

Experimental

General Comments - Melting points were determined with a hot-stage microscope and are uncorrected. Ultraviolet spectra were recorded with a Cary 15 spectrophotometer, ^{1}H NMR spectra were measured using a Varian HA-100 spectrometer, mass spectra and gas chromatographic data were obtained using a DuPont 21-491B mass spectrometer coupled to a Varian Aerograph 2700 gas chromatograph. The glass chromatographic column (2m length x 2mm i.d.) was packed with 1.5% OV-101 on W-HP. Tetrahydrofuran was heated under reflux in the presence of NaH and distilled. *n*-Butyl lithium in hexane was purchased from Aldrich Chemical Company and its concentration determined as described [20]. Thin-layer chromatography was carried out using silica gel G-plates (0.25 mm) developed with mixtures of chloroform and methanol. Elemental analyses were performed by Heterocyclic Chemical Corporation, Harrisonville, Missouri.

Treatment of trimethylsilylpyrimidines with n-butyl lithium in tetrahydrofuran. - To 10 mmol of 5-bromo-2,4-bis N,O-trimethylsilylcytosine [2] (I), 2,4-bis O-trimethylsilyluracil (II) [4] or 5-bromo-2,4-bis N,O-trimethyl-

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* While this report was in press a communication appeared on the anionic rearrangements of trialkylsiloxy benzenes and pyridines (ref.22).

silylisocytosine(III) in 100 ml of freshly distilled tetrahydrofuran at -78° was added dropwise (5 min.) with stirring n-butyl lithium in hexane (for I and III 12.5 ml, 20 mmol; for II 6.25 ml, 10 mmol). The resulting colorless solution was maintained at -78° for one hour; then methanol (~10 ml) was added. The reaction mixture was then evaporated to dryness below room temperature, the resulting residue was dissolved in water and acidified to ~pH 4-5 using 6N hydrochloric acid. In the case of the cytosine derivative (I) the aqueous solution was concentrated and cooled causing cytosine to crystallize. Collection of the product and repetition of this procedure yielded 1.22 g (94%) of cytosine identified by comparison with an authentic sample.

In the cases of the uracil and isocytosine derivatives (II and III respectively) acidification of the aqueous solutions caused precipitation of the 5-trimethylsilyl compounds (IV and V). Following removal of these products, the filtrates were concentrated and uracil (0.38 g, 34%) and isocytosine (0.71 g, 64%) were recovered as described for cytosine.

Reactions at -100° were carried out similarly using ethanol-liquid nitrogen as coolant. Reactions of 25° were begun as described above for -78° reactions. After 15 min. reaction time the reaction mixture was quickly warmed to 25° using a water bath. After 45 min. the products were isolated as described.

5-Trimethylsilyluracil (IV). - Following isolation as described above the crude product was recrystallized from ethanol to yield IV, m.p. 338° (for yields see Table 1). λ_{max}^{MeOH} 261 nm; ^{1}H NMR(DMSO-d_6), δ 0.15 (9H,s), 7.14 (C-4H,s).

Anal. Calc'd for $C_7H_{12}N_2O_2Si$; C, 45.6; H, 6.57; N, 15.2. Found: C, 45.4; H, 6.82; N, 15.3.

2-Amino-5-trimethylsilyl-4-pyrimidinone (5-trimethylsilylisocytosine, (V). - Recrystallization of crude product obtained as described above from ethanol yielded V, m.p. 283° (for yields, see Table 1) which exhibited:

λ_{max}^{MeOH} 291, 228 nm, ^{1}H NMR (DMSO-d_6), δ 0.15 (9H,s), 7.47 (C-4H,s).

Anal. Calc'd for $C_7H_{13}N_3OSi$: C, 45.9; H, 7.15; N, 22.9. Found: C, 45.9; H, 7.34; N, 23.3.

5-Bromo-2,4-bis N,O-trimethylsilylisocytosine(III). – A mixture of 4.5 g of 2-amino-5-bromo-4-pyrimidinone [21], 12 ml of hexamethyldisilazane and 0.15 ml of trimethylchlorosilane was heated under reflux for 12 hours. The reaction mixture was then distilled under reduced pressure to yield 6 g (76%) of 5-bromo-2,4-bis N,O-trimethylsilylisocytosine (III), b.p. 98°/0.16 mm which crystallized on standing. This material was used directly for reaction with *n*-butyl lithium.

Hydrolysis of 5-trimethylsilyluracil (IV). – A solution of .92 g of IV in 50 ml of methanol containing .5 ml of 6N hydrochloric acid was heated under reflux. Aliquots were removed periodically and examined by thin-layer chromatography. After 3 hr. all starting material had disappeared. The solution was then evaporated to dryness and the residue was triturated with a small volume of water. The solid material was collected and dried to yield .44 g (79%) of uracil identified by comparison with an authentic sample.

o-Bromophenylaminotrimethylsilane. – A mixture of 1.72 g (10mmol) of *o*-bromoaniline and 6.44 g (.40 mmol) of hexamethyldisilazane containing a few drops of trimethylsilyl chloride was heated under reflux for 18 hours. *o*-Bromophenylaminotrimethylsilane, b.p. 81-83°/0.4 mm, was distilled from the reaction mixture and used directly. M.s: 245, 243 (M^+); 230, 228 (M^+-Me); 163 (M^+-HBr); 148 (M^+-Me-HBr).

Treatment of bromophenoxytrimethylsilanes with n-butyl lithium. – To a solution of 1.33 g (5.3 mmol) of *o*-, *m*- or *p*-bromophenoxytrimethylsilane [5] in 50 ml of freshly distilled tetrahydrofuran at –78° under nitrogen was added dropwise with stirring 5 ml of *n*-butyl lithium in hexane (8 mmol). The reaction mixture was maintained at –78° for 3 hrs. following addition of n-butyl lithium. Then 15 ml of methanol was added, the solvents were removed *in vacuo*, the resulting residue was dissolved in water and acidified using 6N hydrochloric acid. The acidic solution was extracted with chloroform (3 x 25 ml); the chloroform extract was dried over sodium sulfate and analyzed by gas chromatography/mass spectrometry (gc/ms). Results are tabulated in Table 2.

Treatment of o-bromophenylaminotrimethylsilane with n-butyl lithium. - To a solution of 1.2 g (5 mmol) of *o*-bromophenylaminotrimethylsilane in 50 ml of freshly distilled tetrahydrofuran at -78° under nitrogen was added with stirring 7.5 ml of *n*-butyl lithium in hexane (12 mmol). After addition was complete the reaction mixture was removed from the cooling bath and stirred for an additional 3 hr. The solvent was then removed, the residue was dissolved in aqueous base and extracted with chloroform (3 x 25 ml). The extract was dried over sodium sulfate and analyzed by gc/ms revealing aniline as the only product; no aminophenyltrimethylsilane was detected.

Treatment of phenoxytrimethylsilane and bromobenzene (1:1) with n-butyl lithium. - A solution of 1.7 g (10 mmol) of phenoxytrimethylsilane [6] and 1.6 g (10 mmol) of bromobenzene in 50 ml of freshly distilled tetrahydrofuran was stirred at -78° under nitrogen. To this solution was added 7.5 ml of *n*-butyl lithium in hexane (12 mmol) and these conditions were maintained for 3 hr. after addition was complete. An aliquot was then removed and methylene chloride was added to provide an internal lock resonance for ^{1}H NMR analysis. Two singlet resonances assignable to trimethylsilyl groups with relative intensities 3:7 were observed 5.39 and 5.66 ppm upfield from the internal methylene chloride reference. The resonance appearing 5.39 ppm upfield from internal methylene chloride was identified as that of phenoxytrimethylsilane by addition of authentic material. Gc/ms analysis established that the other trimethylsilylated compound was phenyltrimethylsilane [7].

Acknowledgment.

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