

Article

## Heterocyclic Silyllithium Reagents as Precursors of Masked Hydroxyl Groups. Preliminary Results

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Dados da literatura têm demonstrado que grupos silila substituídos com heterociclos exigem condições de protodesililação consideravelmente mais brandas que as empregadas para o grupo fenildimetilsilila. Comunicamos nesta publicação a preparação do novo reagente 5-metil-2-furildimetilsilil lítio que representa uma possibilidade adicional de incorporação destes grupos silila heterocíclicos.

Heterocycle-substituted silyl groups have been shown to undergo the requisite protodesilylation reaction under much milder conditions than those employed for the phenyldimethylsilyl substituent. We now report the preparation of 5-methyl-2-furyldimethylsilyllithium which represents an additional means for incorporating such heterocyclic silyl groups.

**Keywords:** 5-methyl-2-furyldimethylsilyllithium, protodesilylation, Tamao-Kumada reaction

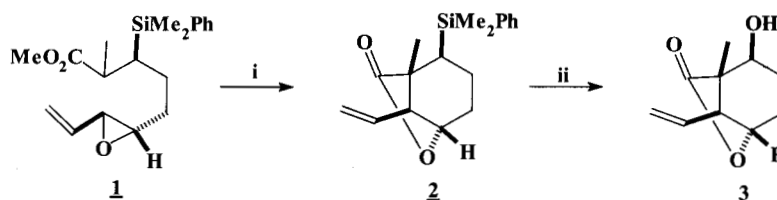
### Introduction

In the course of our studies aiming at the total synthesis of Taxol<sup>1,2</sup>, we prepared the chiral lactone **2**<sup>3,4</sup> (Scheme 1), which might be useful in the construction of the natural product's C-ring. The phenyldimethylsilyl substituent was employed as a hydroxyl group equivalent because it was the only one that allowed the cyclisation of allylic epoxide **1**. The needed conversion of **2** into hydroxylactone **3** required two steps: exchange of the phenyl group for fluorine (protodesilylation) and oxidative substitution of the generated fluorodimethylsilyl group by hydroxyl group, the so-called Tamao-Kumada reaction<sup>5,6</sup>. Nevertheless, the first reaction proved to be troublesome and was only attained

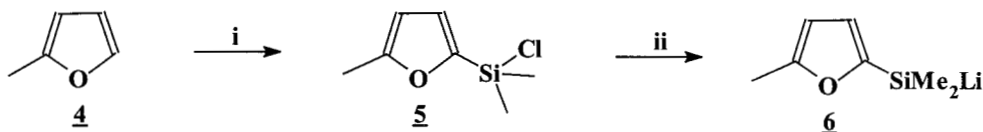
through forcing conditions. For this reason, the overall yield of the hydroxyl group introduction was just reasonable.

In the work of total synthesis of reserpine developed in our group<sup>7</sup>, we had also faced difficulties in proceeding that first step. Then, we envisaged that a heterocyclic aromatic substituent on silicon could undergo protodesilylation more easily. Thus, the 2-furyldimethylsilyl group was devised as an alternative to phenyldimethylsilyl group. Indeed, the mentioned transformation was carried out under surprisingly mild conditions (TBAF, THF).

Therefore, we wondered how efficiently a furylsilyl analog of **2** would have its furyl moiety replaced by fluorine. Our synthetic approach to lactone **2** required that the



**Scheme 1.** i - LHMDS, HMPA, THF, -30 °C - r.t. ii - a) HBF<sub>4</sub>.OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 70 °C (sealed tube); b) KF, MCPBA, DMF, r.t., 50% (2 steps).



**Scheme 2.** i - a) BuLi, Et<sub>2</sub>O, -78 °C, r.t., reflux. b) Me<sub>2</sub>SiCl<sub>2</sub>, Et<sub>2</sub>O, -78 °C, 0 °C, r.t. ii - Li<sup>+</sup>, THF, -10 °C.

furylsilyl group be introduced as an anionic species. Thus, we sought the preparation of the desired furylsilyllithium.

## Results and Discussion

The preparation of the target reagent started with 2-methylfuran **4** (Scheme 2), which is deprotonated with BuLi and coupled with Me<sub>2</sub>SiCl<sub>2</sub>. The produced chlorosilane **5** is then treated with lithium in THF at -10 °C, the same procedure employed in the preparation of PhMe<sub>2</sub>SiLi<sup>8,9</sup>, leading to 5-methyl-2-furyldimethylsilyllithium **6**. However, we have noticed that the lithium-chlorine exchange for **5** is much slower than the one observed in the preparation of PhMe<sub>2</sub>Li which takes less than 2 days at the same temperature. Even after a week at those conditions, the concentration of **6** remained considerably lower than it was expected. The reaction flask was then stored in a refrigerator for 2-3 weeks. Fortunately, after that time, the solution of **6** achieved a satisfactory molarity. The methyl substituent at the 5-position of the furan ring was set in order to prevent a reagent self-deprotonation.

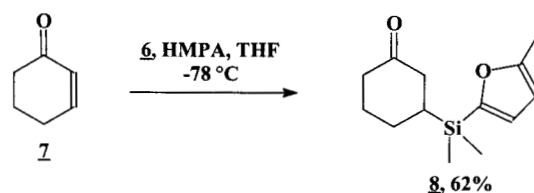
The novel reagent was reacted with 2-cyclohexenone **7**, which afforded the 3-silylcyclohexanone **8** (Scheme 3).

Since the introduction of the 2-furyldimethylsilyl group in synthesis by our group<sup>7</sup>, a few examples of heterocyclic aromatic-substituted silyl groups have been reported in the literature<sup>6,10,11</sup>, but the present work has been the first to present the correspondent silyllithium. In all cases, the heterocyclic aromatic moiety can be knocked out under milder conditions than those usually applied to phenyldimethylsilyl substituent. Kociensky and coll. have even employed the same 5-methyl-2-furyldimethylsilyl group in the synthesis of the C-26-C-32 fragment of rapamycin<sup>10</sup>. Furthermore, they have shown that the replacement of the furyl substituent can be effected by a photooxidation under a very mild condition.

It has been found that the novel reagent is not as stable as phenyldimethylsilyllithium. It must be used as soon as it is prepared, which is obviously a drawback. At the moment, we are seeking an improvement of the reagent that might enable one to stock it. Applications of the novel reagent or its analogs will be reported at an appropriate time.

## Conclusion

We have introduced the novel 5-methyl-2-furyldimethylsilyllithium, which was reacted with 2-cyclohexenone leading to the expected conjugate addition



**Scheme 3.**

product. Reports in the literature have shown that substances with such silyl group lead to the protodesilylation products under very mild conditions. That makes the establishment of the furylsilyl substituent via a lithium species particularly valuable.

## Experimental

### General

2-methylfuran (Aldrich) and Me<sub>2</sub>SiCl<sub>2</sub> (Fluka) were used as purchased. The solvents were dried with the Na<sup>0</sup>/benzophenone system and distilled. HMPA was dried with CaH<sub>2</sub> and distilled under high vacuum. Column chromatography (flash)<sup>12</sup> was performed with 230-400 mesh, 60A (Merck) silica gel. <sup>1</sup>H-NMR spectra were recorded on a Varian VXR-200 (200 MHz). The chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Mass spectra [electron impact (EI) or chemical ionization (CI)] were obtained on a Nermag R10-10, while the high resolution mass spectrum (Fast Atom Bombardment - FAB) on a JEOL JMS-DX 303 HF. The infrared spectrum (IR) was recorded on a Perkin-Elmer 1600 FTIR Series.

### 5-methyl-2-furyldimethylsilylchloride **5**

A stirred solution of 10.0 g of 2-methylfuran (0.121 mol) in 200 mL of ether under argon at -78 °C is treated with 46 mL of a 2.5 M solution of BuLi (0.95 equiv.) in hexanes. The mixture is allowed to warm up to room temperature and then it is refluxed for 3 h. After that time, the mixture is transferred to another flask containing a stirred solution of 73 mL of Me<sub>2</sub>SiCl<sub>2</sub> (5.0 equiv.) in 300 mL of ether at -78 °C under argon. After 20 min under this condition, the dry ice bath is replaced by another one of ice-water. At 0 °C, the reaction is maintained for 1 h and then, it is allowed to reach room temperature. The stirring is stopped so that the produced precipitate go down to the flask bottom. The ethereal solution is transferred through a canula to another flask and the solvents are distilled under

argon. The crude product (15.5 g) is employed in the following reaction.  $^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  6.72 (d, 1H), 6.01 (d, 1H), 2.39 (s, 3H), 0.69 (s, 6H). Mass spectrum (EI)  $m/z$  (rel. intensity) : 174 ( $\text{M}^+$ , 58), 159 (100), 139 (17), 95 (83), 93 (25).

#### 5-methyl-2-furyldimethylsilyllithium **6**

3.07 g of lithium (wire, Aldrich) is quickly added to a stirred solution of 15.5 g of crude silane **5** (0.0887 mol) in 100 mL of THF under argon. The obtained heterogeneous mixture remains under the mentioned condition for 4 days. The resulting red mixture is titrated by the same methodology employed by Fleming *et al.*<sup>9</sup> The concentration of **6** was found to be 0.17 M, naturally much lower than expected. The reaction flask was then placed in a refrigerator ( $\sim -10$  °C). After 2-3 weeks, the THF solution was again titrated. The silyllithium concentration was 0.71 M.

#### 3-(5-methyl-2-furyldimethylsilyl)-cyclohexanone **8**

2-cyclohexenone (0.051 mL, 0.519 mmol) is added to 3.0 mL of a stirred 0.71M solution of 5-methyl-2-furyldimethylsilyllithium (4.0 equiv.) in THF at  $-78$  °C under argon, containing 0.37 mL of HMPA. After 20 min, a concentrated aqueous solution of  $\text{NH}_4\text{Cl}$  is added. The product is extracted with hexanes and the organic layer is washed once with water. The crude product is purified by flash column chromatography (7% ethylacetate/hexanes). Yield: 0.078 g (62%).  $^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  6.46 (d, 1H), 5.95 (d, 1H), 2.29 (s, 3H), 2.00-2.40 (4H), 1.10-1.90 (5H), 0.30 (s, 3H), 0.08 (s, 3H). IR ( $\text{cm}^{-1}$ ) : 2941, 1712, 1248, 1018, 829, 784. Mass spectrum ( $\text{NH}_3$ )  $m/z$  (rel. intensity) : 236 ( $\text{M}^+$ , 10), 213 (25), 197 (11), 155 (18), 139 (35), 81 (54), 75 (100). High resolution mass spectrum (FAB) : found : 236.1239, calculated ( $\text{C}_{13}\text{H}_{20}\text{O}_2\text{Si}$ ,  $\text{M}^+$ ) : 236.1233.

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