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Bis(2-thienyl)silanes: new, versatile precursors to arylsilanediols

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Abstract—Silanediols have been shown to be effective bioisosteres for the hydrated carbonyl group. Current methods for the formation of silanediols place a number of constraints on how and where this functionality may be used. A range of arylsilanes that would allow both the formation of arylsilanediols and that are also compatible with multi-step synthetic routes, have been investigated as possible precursors to silanediols. Through this study bis(2-furyl)silanes and, in particular, bis(2-thienyl)silanes have been identified as practical precursors to arylsilanediols.

Silicon has a rich chemistry, however this has largely been restricted to its use as a controlling element in the formation of conventional carbon based structures.[1] The use of silicon-containing groups in biological research, and in particular drug discovery, has been known for some time. Enhanced lipophilicity, pro-drug development or as alternatives for tetrahedral carbon/nitrogen atoms have all provided potential avenues for the inclusion of silicon (e.g., see Fig. 1).[2–4]

Included in this effort has been the recent application of silicon based groups as isosteres of transient functionality when it is associated with functional groups responsible for biological activity.[5,6] The most notable example of this is the application of silanediols as bioisosteres of the hydrated carbonyl group. To date this has largely been restricted to species such as **5** as mimics of the hydrated amido group, **4** (Fig. 2) and their application in the development of peptidomimetics as protease inhibitors.[7–11]

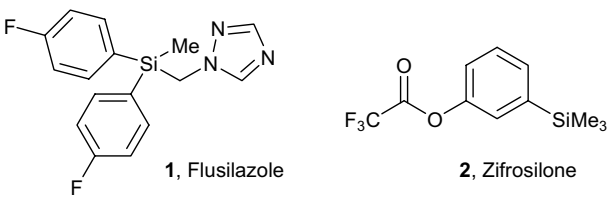

Figure 1. Silicon-containing bioactive compounds.

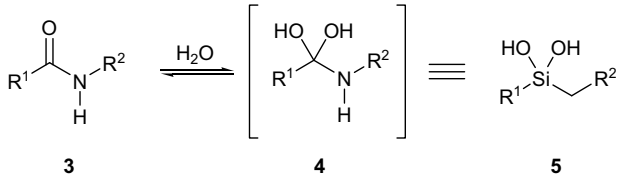

Figure 2. Silanediols as mimics for the hydrated amido group.

Our interest in silicon bioisosteres, as alternatives to aromatic carbonyl species, required a precursor for silanediols that was stable to conventional synthetic procedures and purification techniques yet may be removed under mild conditions when required. A range of silicon based functionality has successfully been employed as precursors to silanols (SiOR, Si–halogen, SiH) however, the corresponding reactivity profile is not compatible with a multi-step total synthesis. Phenylsilanes are the one precursor that has received widespread use, has demonstrated the desired stability, yet may liberate silanols under appropriate conditions. The nature of other functionalities present in these increasingly complex systems has highlighted some limitations of this approach[6,12] and during the course of this work an alternative has been developed to address some of these concerns.[13,14]

Aromatic amides are a common motif found in both synthetic and naturally occurring biologically active compounds (e.g., see Fig. 3).[15–20] The corresponding silanediol bioisosteres represent an important class of target for both the discovery of new bioactive structures

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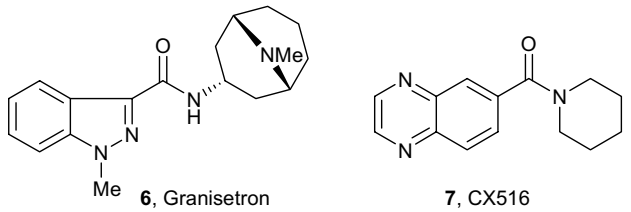


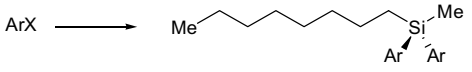
Figure 3. Biologically active aryl amides.

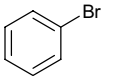
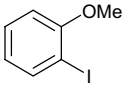
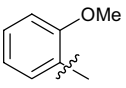
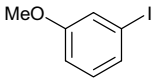
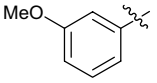
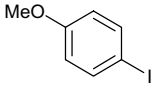
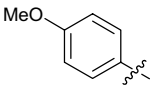
and as potential derivatives of current products to combat the observed increasing levels of resistance. As a result, aromatic amides, and more generally aromatic carbonyl compounds, highlight a major obstacle in the use of diphenylsilanes as silanediol precursors—the preparation of arylsilanediols using this methodology is therefore extremely limited.

Eaborn[21,22] and others[23] have demonstrated that the rate of hydrolysis of aryl–silicon bonds was dependent on the nature of the aromatic substituents. On this basis, and in light of our practical constraints, we now wish to report the synthesis of a range of diarylsilanes, subsequent hydrolysis of the aryl–silicon bonds and hence their potential as precursors to silanediols.

The desired diaryldialkylsilanes were prepared in good yields (typically $>80\%$) by the addition of a slight excess of the appropriate aryllithium reagent to the dialkyldichlorosilane. Purification by short-path distillation led to much reduced yields of analytically pure material (Table 1). Although sterically demanding aryl groups have also been shown to be susceptible to hydrolysis[22] the generation of dimesitylsilanes by the addition of 2 equiv of mesityllithium (generated from bromomesitylene and *n*-butyllithium) proved problematic in our hands[24] and exploitation of this form of control was discontinued.

Table 1. Formation of diarylmethyloctylsilanes[a]



Entry	ArX	Ar	Yield[b] (%)
1			**8**, 44
2			**9**, 31
3			**10**, 52
4			**11**, 24
5			**12**, 36
6			**13**, 77

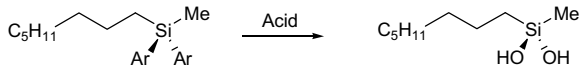
[a] ArX (3.0 equiv), ^{n}BuLi (2.5 equiv), THF, −78 °C, 30 min then dichloromethyloctylsilane (1.0 equiv).
[b] Yield after short-path distillation.

The susceptibility of the diarylsilanes to acid hydrolysis was then investigated (Table 2). The acids studied were triflic acid, which is currently used in the hydrolysis of Si–Ph bonds, TFA, as this is used routinely to remove protecting groups (e.g., Boc) and silica gel to establish the stability to chromatography. As expected the Ph–Si bond was hydrolysed in the presence of triflic acid but was found to be stable to both TFA and silica gel. The electron-rich aromatic rings (Table 2: entries 2 and 4) were extremely sensitive and gave the silanediol (as a mixture, by ESI mass spectrometry, with a range of siloxanes) under all of the conditions examined. Surprisingly the 3-methoxyphenyl group was only removed by the action of triflic acid. Both heteroaromatic examples (Table 2: entries 5 and 6) exhibited the desired profile of being stable to silica gel yet could be removed under mild acidic conditions. These results coupled with the increased ease of synthesis and purification led to the 2-thienyl derivative being selected as the precursor of choice.

To confirm that this approach would allow the formation of phenylsilanediols by the selective hydrolysis of the silicon-2-thienyl bond the silanes **17** and **18** were prepared[25] and treated with TFA.[26] This led to the desired phenylsilanols being produced with no evidence, by NMR, for the 2-thienylsilicon bond remaining intact (Scheme 1).

In conclusion, bis(2-thienyl)silanes and bis(2-furyl)silanes have been shown to be stable to chromatography yet undergo hydrolysis under mild acidic conditions and are therefore suitable precursors to silanediols, and in particular phenylsilanediols. Application to the preparation of biologically active materials bearing arylsilandiol bioisosteres will be reported elsewhere.

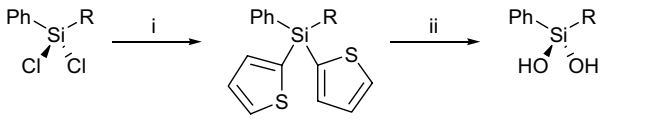
Table 2. Hydrolysis of diarylmethyloctylsilanes[a]



8 - 13 **14**

Entry	Substrate	Acid[b]		
		Silica (%)	TFA (%)	TfOH (%)
1	**8**	[b]	[b]	85
2	**9**	84	90	91
3	**10**	[b]	[b]	87
4	**11**	88	85	85
5	**12**	[b]	80	82
6	**13**	[b]	85	84

[a] Formation of **14** using silica (500 mg), TFA (5.0 equiv) or TfOH (2.5 equiv), DCM, 0 °C, 2 h then NH_4OH (aq).
[b] Refers to complete recovery of starting material.



15 R=Me
16 R=Ph

17 R=Me, 55%
18 R=Ph, 84%

19 R=Me, 81%
20 R=Ph, 86%

Scheme 1. Reagents and conditions: (i) 2-thienyllithium, THF, −78 °C, 18 h; (ii) TFA, DCM, 0 °C, 2 h then NH_4OH (aq).

Acknowledgement

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25. Bis(2-thienyl)diphenylsilane **18**: 2-Thienyllithium (10.0 mL of a 1.0 M solution in THF, 10.0 mmol) was added dropwise over 10 min to a solution of dichlorodiphenylsilane (1.27 g, 5.0 mmol) in THF (50 mL) at −78 °C. The mixture was then allowed to warm to room temperature overnight after which the solvent was removed in vacuo. Dichloromethane (50 mL) was added and any precipitate removed by filtration. The filtrate was washed with water (3 × 30 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude product. Recrystallisation gave **18** as a white crystalline solid (1.46 g, 4.2 mmol, 84%); mp 132–134 °C (from ethyl acetate); (found C, 69.14; H, 4.79. $C_{20}H_{16}S_2Si$ requires C, 68.92; H, 4.63); silica gel TLC R_f 0.40 (petrol); ν_{max}/cm^{-1} (KBr) 3071, 2958, 2922, 1427, 1213, 1108; δ_H (300 MHz; $CDCl_3$) 7.80 (2H, t, H5′ *J* 4 Hz), 7.68 (4H, d, H2/H6 *J* 8 Hz), 7.45 (8H, m, H3/H3′/H4/H5), 7.26 (2H, t, H4′ *J* 4 Hz); δ_C (75 MHz; $CDCl_3$) 138.86 (C5′), 136.22 (C2/C6), 134.38 (C1), 133.89 (C2′), 133.22 (C3′), 130.53 (C4), 128.77 (C4′), 128.37 (C3/C5); *m*/*z* (EI) 348 (M^+, 14%), 271(20), 105(37), 77(100). [Found M^+, 348.0459. $C_{20}H_{16}S_2Si$ requires 348.0457.]
26. Diphenylsilanediol **20**: Trifluoroacetic acid (0.38 mL, 5.0 mmol) was added dropwise over 5 min to a solution of **18** (0.35 g, 1.0 mmol) in dichloromethane (30 mL) at 0 °C. After stirring for 2 h, ammonia (30% aq) was added dropwise until the solution was neutral pH. The solvents were removed in vacuo, to give the crude product as a yellow/brown solid, which was purified by recrystallisation to give **20** as a white crystalline solid (0.19 g, 0.86 mmol, 86%); mp 160–162 °C (from benzene) lit.,[27] 160–162 °C (dec); silica gel TLC R_f 0.15 (1:9, acetone–petrol); ν_{max}/cm^{-1} (KBr) 3412, 2987, 1641, 1445, 1392, 1142; δ_H (300 MHz; $CDCl_3$); 2.20 (2H, br s, Si(O*H*)$_2$), 7.36–7.47 (6H, m, H3/H4/H5), 7.65–7.68 (4H, m, H2/H6); δ_C (75 MHz; $CDCl_3$); 128.66 (C3/C5), 131.17 (C4), 133.73 (C2/C6), 136.32 (C1).
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