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# Synthesis of α- Alkoxysilanes: Birch Reduction of 2-Trialkylsilylfurans

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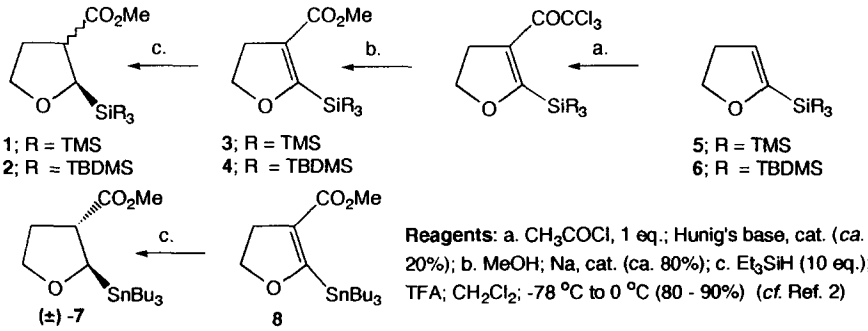
**Abstract:** The Birch reduction of (2 -trialkysilyl)furan-3-carboxylic acids has been applied to the synthesis of methyl (2-trialkylsilyl)tetrahydrofuran-3-carboxylates. It is believed that the silicon moiety in such substrates controls the sense of asymmetric induction observed in Michael reactions of the derived enolates with methyl cinnamate. Mild oxidative removal of the silicon moiety generates an oxonium cation which undergoes nucleophilic capture to afford a functionalised furanopyran.

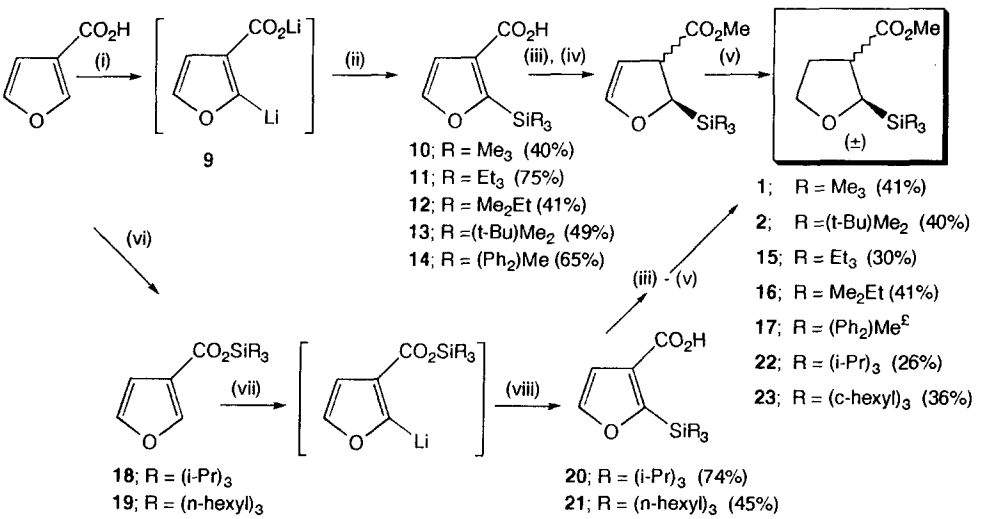

As a continuation of our[1] studies into the use of α - heterofunctionalised organometallics in organic synthesis we wished to prepare the tetrahydrofuran derivatives **1** and **2**. Initially, we sought to apply the route which we[2] have developed for the synthesis of the analogous stannane **7** which involved ionic reduction[3] of the corresponding vinylstannane **8**. Although ionic reduction of the silanes **3** and **4** was indeed possible the overall efficiency and utility of the sequence as outlined in **Scheme 1** was marred due to the capricious nature of the acylation reactions of silanes **5** and **6** and our difficulties experienced in removing excess triethylsilane from the desired esters **1** and **2** after the reduction step[4]. Having been thwarted in our attempts to prepare the silanes **1** from dihydrofuran an alternate strategy for their preparation in multigram quantities was sought.




**Scheme 1**

Although the Birch reduction[5] of furan-3-carboxylic acid was first reported in 1975 by Kinoshita [6] synthetic applications of this reduction sequence have received scant attention[7]. Similarly the Birch reduction of arylsilanes has been known for some time[8], but to the best of our knowledge has been restricted to carbocyclic aromatic systems[9]. From a consideration of the known directing effect of silicon substituents in Birch[5a] and related[10] reduction reactions we anticipated that a silicon substituent at C-2 in furan-3-carboxylic acid would act in a synergistic sense with the carboxylic acid functional group and provide access to (2-trialkylsilyl-2,3-dihydrofuran-3-yl)carboxylic acids.

The requisite (2-trialkylsilyl)-3-furoic acids were readily prepared using the methodology previously developed by Knight[11] and Keay[12]. Treatment of 3-furoic acid with LDA (2.2 eq.; THF; -78 °C; 30 mins.), presumably to generate the di-anion **9**, followed by the addition of the appropriate chlorosilanes afforded, after acidic work-up, the desired silylfuroic acids **10** - **14** in good overall yield, **Scheme 2**. Notable exceptions to this generalisation however include trapping of the di-anion **9** with $(i\text{-Pr})_3SiCl$ or $(n\text{-hexyl})_3SiCl$ which resulted in the isolation of the silanes **20** and **21** in 7% and 1% yield respectively. In these cases conversion of 3-furoic acid to the corresponding silyl esters (1.2 eq. chlorosilane; 2.5 eq. imidazole; DMF; 100 °C; 16 hours **or** 1.2 eq. chlorosilane; DBU, 1.2 eq.; $CH_2Cl_2$; 2 hours and subsequent aqueous work-up; essentially quantitative yield) followed by mono-anion generation (1.2 eq. LDA; 1.2 eq. HMPA; THF; -78 °C, 15 mins.) and silatropic rearrangement[13] afforded the desired silanes **20** and **21** in 74% and 45% overall yield respectively, **Scheme 2**.



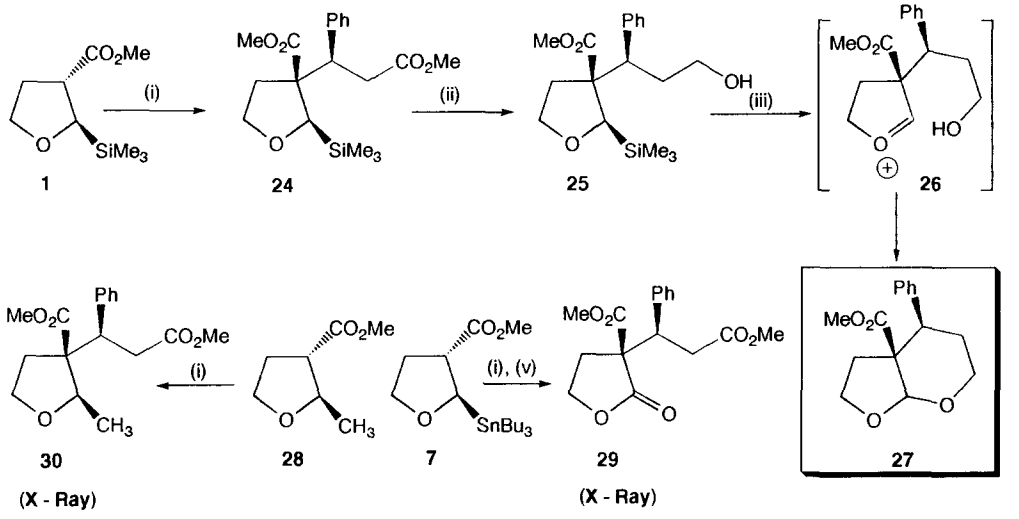

(£ Complex mixture of products obtained, *c.f.* ref. 9b)

**Reagents and conditions:** (i) LDA, 2.2 eq.; THF; -78 °C; 30 mins.; (ii) a. $R_3SiCl$; b. 2M HCl; (iii) a. Na, 3 eq.; $NH_3$, propan-2-ol; -35 °C, b.$NH_4Cl$; -33 °C; (iv) $CH_2N_2$; $Et_2O$; (v) 10% Pd/C; EtOH; $H_2$, 1 atm.; (vi) $R_3SiCl$, 1.1 eq; DBU, 1 eq.; $CH_2Cl_2$; 20 °C **or** $R_3SiCl$, 1.2 eq.; imidazole, 2 eq.; DMF; 100 °C; (vii) LDA, 1.2 eq.; THF - HMPA (1:1; v/v); - 78 °C; (viii) 2M HCl.

**Scheme 2**

Having prepared a number of substrates we were now in a position to investigate their reduction using standard Birch reduction conditions. Dissolution of the carboxylic acids in liquid ammonia followed by the addition of propan-2-ol[6] and sodium metal (3.3 eq.) generated a deep-blue coloured solution, which was quenched at -35 °C with ammonium chloride. After removal of the ammonia, the crude products were dissolved in diethylether and converted to their respective methyl esters by treatment with diazomethane. The crude methyl esters were then redissolved in methanol and reduced under an atmosphere of dihydrogen using 10% palladium on charcoal as catalyst. Purification at this stage, either by column chromatography or vacuum distillation, afforded the desired esters[14] in *ca.* 40% overall yield from the corresponding furoic acid derivatives. In practice we have found that the overall sequence is relatively clean, requires only one purification step, and can be readily performed on a multigram scale (typically 50 mmol). Unfortunately reduction of the phenylsilane **17** produced a complex reaction mixture, presumably due to competing reduction of the phenyl and furan rings[9b].

An underlying motive for undertaking these studies is to determine the effect, if any, of organometallic residues upon the stereochemistry of enolate generation and to utilise the innate chemical reactivity of the carbon - "metal" bond at further stages in a synthetic sequence. Treatment of the ester **1** with LDA (1.1 eq., THF, -78 °C; 30 mins.) followed by the addition of methyl cinnamate (1.5 eq.) and subsequent low temperature quench ($NH_4Cl$; -78 °C) generated a single *syn* Michael adduct **24** in 40% yield isolated together with the *trans* isomer of the starting material (30%). It is to be noted that the enolates derived from **7** and **28** also afford the *syn* Michael adducts **29** and **30** whose stereostructures have been unambiguously confirmed[15] by X - ray diffraction studies, (**Scheme 3**): rationalisation of these observations is the focus of current investigations.




**Reagents and conditions:** (i) a. LDA, 1.1 eq.; THF; -78 °C; 30 mins., b. methyl cinnamate, 1.5 eq.; THF; -78 °C; 30 mins., c. $NH_4Cl$ aq.; -78 °C; (ii) DIBAL-H, 2.2 eq.; THF; -78 °C; (iii) CAN, 2.2 eq.; AcOH; 60 °C, 5hrs.; (iv) $O_3$; $CH_2Cl_2$; -78 °C (ref. 15).

**Scheme 3**

Reduction of **24** (DIBAL - H, 2.2 eq.; THF; -78 °C) proceeded at the less hindered ester group and afforded the alcohol **25** in 77% isolated yield. We anticipated[16] that at this stage chemoselective oxidation of the

α-alkoxymethysilyl moiety of **25** could be achieved, generating an oxonium cation **26** which would undergo nucleophilic capture to the bi-cyclic system **27**. Indeed, in an unoptimised sequence, treatment of the silane **25** to oxidation with CAN[17] (2.1 eq.) in warm acetic acid (60 °C) afforded the furanopyran[18] **27** in 40% yield after column chromatography, **Scheme 3**.

In conclusion, we have demonstrated that α-alkoxymethylsilanes may be readily prepared from 3 - furoic acid using a novel Birch reduction, that the products of these reactions undergo diastereoselective Michael reactions[19] and that the silicon group can be removed under mild oxidative conditions to generate an oxonium cation which is capable of intramolecular nucleophilic capture. Synthetic applications of this general sequence are now underway and will be reported in due course.

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