THE REGIOSPECIFIC FORMATION AND REACTIONS OF 4-LITHIO-2-(t-BUTYL-
DIMETHYLSILYL)-3-(HYDROXYMETHYL)FURAN: AN APPROACH TO 3,4-DISUBSTITUTED FURANS

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Summary: 4-Lithio-2-(t-butyldimethylsilyl)-3-(hydroxymethyl)furan , generated
by treating 2-(t-butyldimethylsilyl)-3-(hydroxymethyl)furan 2 with 2.2 equiva-
lents of n-butyllithium (DME/0°C/15 min), is trapped by a variety of electro-
philes to produce, after desilylation, 3,4-disubstituted furans in good to
moderate yields.

The propensity of furan to both lithiate and add electrophiles at the C-2
or C-5 position has led chemists to develop elaborate methods for preparing
3,4-disubstituted furans. Some of these include Diels-Alder--Retro-DielsAlder
chemistry[1], chemical modifications of 3,4-bis(acetoxymethyl)furan[2] or
3,4-furandicarboxylic acid[3] and the preparation of 3-iodo-4-methylfuran from
2-butyne-1,4-diol[4]. We herein report a more versatile synthesis of 3,4-disub-
stituted furans in which both the C-3 and C-4 substituents can be modified for
later synthetic applications.

The lithiation of 2,3-disubstituted furans has been reported to produce
the C-5 lithio species exclusively[5] due to the increased acidity of the
α-protons over the β-protons on heteroaromatic compounds[6]. We envisioned,
however, that if the group at C-2 was sterically cumbersome and the substituent
at C-3 was an ortho-lithiation director, that lithiation might occur at C-4 due
to preferential base co-ordination to the C-3 group rather than with the
sterically blocked furan ring oxygen. To satisfy these requirements we chose
the t-butyldimethylsilyl group as the bulky C-2 substituent and a hydroxymethyl
group (at C-3) as the lithiation director[7] (compound 2, Scheme 1).

SCHEME 1
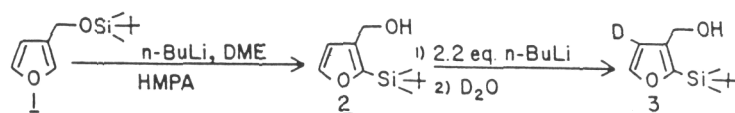
Lithiation of 3-[(t-butyldimethylsilyl)oxymethyl]furan $\underline{1}$ (n-BuLi/HMPA/ -20°C/DME) provided the prerequisite material, 2-(t-butyldimethylsilyl)-3- (hydroxymethyl)furan $\underline{2}$, via a 1,4 O->C silyl migration[8](Scheme 1). Treatment of $\underline{2}$ with 2.2 equivalents of n-butyllithium (HMPA/DME/-20°C/1h) and quenching the resulting anion with MeOD produced the 4-deuterio species $\underline{3}$ (>95% by ^{1}HNMR). That the deuterium had indeed added at C-4 was confirmed by ^{1}HNMR; of the two furan ring protons in the ^{1}H NMR spectrum of compound $\underline{2}$ (δ7.57 (H-5) and δ6.45(H-4)), the upfield signal had disappeared in the ^{1}H NMR spectrum of $\underline{3}$[9].

Optimized results were obtained by treating $\underline{2}$ with 2.2 equivalents of n-butyllithium in DME (without HMPA) at 0°C for 15 minutes; quenching the resulting anion with a variety of electrophiles in the presence of LiCl (15 equivalents)[10] produced 2,3,4-trisubstituted furans in moderate to good yields (Table 1). The products of these additions were desilylated ((n-Bu)$_4$NF/THF) to afford 3,4-disubstituted furans in excellent yields. In the case of entries 6 and 7, competing reactions with the hydroxymethyl group occured, therefore, excess electrophile was added to produce the C- and O-alkylated products $\underline{8}$ and $\underline{9}$. The resulting carbonate and urethane were cleaved prior to desilylation[11].

Table 1: Preparation of 3,4-Disubstituted Furans
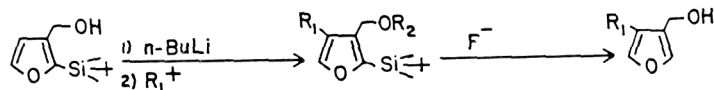
	Electrophiles	Product(% Yield)	Product(% Yield)
1.	DOCH$_3$	$\underline{3}$ R$_1$=D, R$_2$=H (95)	$\underline{10}$ (92)
2.	I$_2$	$\underline{4}$ R$_1$=I, R$_2$=H (92)	$\underline{11}$ (91)
3.	ICH$_3$	$\underline{5}$ R$_1$=CH$_3$, R$_2$=H (82)	$\underline{12}$ (90)
4.	(CH$_3$)$_3$SiCl	$\underline{6}$ R$_1$=Si(CH$_3$)$_3$, R$_2$=H (78)	-- --
5.	Cl(CH$_2$)$_3$I	$\underline{7}$ R$_1$=(CH$_2$)$_3$Cl, R$_2$=H (66)[a]	$\underline{13}$ (94)
6.	ClCOOCH$_3$	$\underline{8}$ R$_1$=R$_2$=COOCH$_3$ (57)	$\underline{14}$ (91)
7.	ClCON(CH$_2$CH$_3$)$_2$	$\underline{9}$ R$_1$=R$_2$=CON(CH$_2$CH$_3$)$_2$ (75)	$\underline{15}$ (90)

a) yield based on recovered starting material

A general experimental procedure follows. A solution of $\underline{2}$ (0.25 g, 1.2 mmol) in DME (5 mL) was cooled to -78°C under argon and treated with n-butyl-lithium (1.04 mL of 2.5 M in hexane, 2.6 mmol). The solution was stirred at 0°C for 15 minutes and then treated with anhydrous lithium chloride (0.50g, 12 mmol) followed immediately by iodomethane (0.37 mL, 6.0 mmol). The solution was stirred at 0°C for 24 hours and then treated with saturated aqueous ammonium chloride. An ethyl acetate extraction, silica gel column and a distillation afforded $\underline{5}$ (82%).

Compound $\underline{5}$ (1 eq.) was then stirred with tetra-n-butylammonium fluoride (2 eq.) in anhydrous THF for 12 hours under argon. Normal workup afforded

3-(hydroxymethyl)-4-methylfuran 12 (90%) after purification[12].

The reaction was not limited to the C-2 substituted t-butyldimethylsilyl furan 2 and was found to proceed favourably with other C-2 silyl substituted furans (Table 2). Replacement of the silane by a significantly smaller methyl group resulted in a 2:1 ratio of C-4:C-5 anions (entry 7, Table 2)[13]. These results tend to indicate that the steric bulk of the silane moiety is effectively blocking base co-ordination to the furan ring oxygen, thus allowing co-ordination of the base to the hydroxymethyl group at C-3 which ultimately results in C-4 deprotonation. However, Table 3 and entry 6 of Table 2 indicate that factors other than just steric bulk are involved as a change of solvent, additives and/or temperature can vary the C-4:C-5 anion ratio. Interestingly, the bidentate solvent DME does not require HMPA to produce a favourable anion ratio, thus, solvent coordination to the base and/or the dianion of 2 must be one of the contributing factors.

Table 2: The Effect of C-2 Substituents on C-4:C-5 Anion Ratios[a]
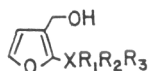
	Compound	Temperature(^{O}C)	C-4:C-5 Anion Ratio[b,c]
1.	X=Si, R_1=R_2=$R_3 \approx$ Me	-20 or 0	100 : 0
2.	X=Si, R_1=R_2=Me, R_3=i-Pr	-20 or 0	100 : 0
3.	X=Si, R_1=R_2=Me, R_3=t-Bu	-20 or 0	100 : 0
4.	X=Si, R_1=R_2=Ph, R_3=t-Bu	-20 or 0	100 : 0
5.	X=Si, R_1=R_2=$R_3 \approx$ i-Pr	-20	100 : 0
6.	X=Si, R_1=R_2=$R_3 \approx$ i-Pr	0	75 : 25
7.	X=C, R_1=R_2=$R_3 \approx$ H	-20 or 0	64 : 36

a) all reactions were performed in DME for 1 hour using 2.2 equivalents of n-butyllithium as the base followed by a MeOD quench of the anion.

b) ratio determined by integration of the ^{1}H NMR spectrum.

c) ratio was adjusted for the %H content of the MeOD as determined by M.S..

Table 3: Solvent Effects on the C-4:C-5 Anion Ratio of Furan 2[a]

	Solvent System	C-4 : C-5 Anion Ratio[bc]
1.	Hexane	70 : 30
2.	Hexane / HMPA	66 : 34
3.	Et_2O	68 : 32
4.	Et_2O / HMPA	100 : 0
5.	THF	75 : 25
6.	THF / HMPA	100 : 0
7.	DME and DME / HMPA	100 : 0

a) all reactions were performed at -20°C for 1 hour using n-butyllithium as the base followed by a MeOD quench. b) determined by ^{1}H NMR integration.

c) ratio was adjusted for the %H content of the MeOD as determined by M.S..

Thus we have developed a short and efficient synthesis of 3,4-disubstituted furans from readily available 3-[(t-butyldimethylsilyl)oxymethyl]furan **1**. Work is continuing to expand the scope of these lithiations and applications of this methodology to the synthesis of furan-containing natural products is in progress.

ACKNOWLEDGEMENTS

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9. The 5-deuterio-2-(t-butyldimethylsilyl)-3-(hydroxymethyl)furan **16** was prepared as follows:
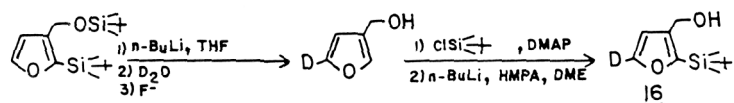
The downfield furan proton of compound **2** (δ 7.57) was absent in the ^{1}H NMR spectrum of **16**.

10. Yields were substantially increased in the presence of lithium chloride, see: Carpenter, A.J.; Chadwick, D.J. Tetrahedron Lett., 1985, 26, 5335.

11. The carbonate **8** was removed by K_2CO_3/MeOH/1h/r.t. and the urethane **9** was removed by NaOMe/MeOH/60°C/12h.

12. Compound **12**: b.p. 91-93°C/20 mm; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.02 (s, 3H), 3.21 (bs, 1H), 4.49 (s, 2H), 7.15(s, 1H), 7.32 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 7.8, 55.5, 119.5, 125.3, 140.2, 140.6; M.S. 112.

13. 2-Methyl-3-furancarboxylic acid was prepared according to reference 2a and then reduced with lithium aluminum hydride in ether to provide 3-(hydroxymethyl)-2-methylfuran in 93% yield.

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