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

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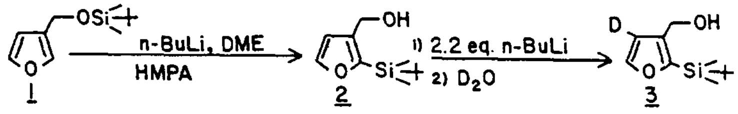
Summary: 4-Lithio-2-(t-butyldimethylsilyl)-3-(hydroxymethyl)furan , generated by treating 2-(t-butyldimethylsilyl)-3-(hydroxymethyl)furan 2 with 2.2 equivalents of n-butyllithium (DME/0^{o}C/15 min), is trapped by a variety of electrophiles to produce, after desilylation, 3,4-disubstituted furans in 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-disubstituted 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).

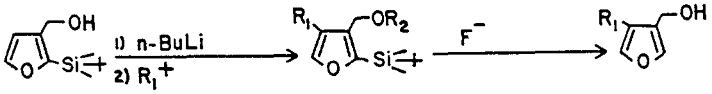
SCHEME 1



Lithiation of 3-[(t-butyldimethylsilyl)oxymethyl]furan 1 (n-BuLi/HMPA/-20°C/DME) provided the prerequisite material, 2-(t-butyldimethylsilyl)-3-(hydroxymethyl)furan 2, via a 1,4 O->C silyl migration[8](Scheme 1). Treatment of 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 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 2 (δ7.57 (H-5) and δ6.45(H-4)), the upfield signal had disappeared in the ^{1}H NMR spectrum of 3[9].

Optimized results were obtained by treating 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 8 and 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$_3$	3 R$_1$=D, R$_2$=H (95)	10 (92)
2.	I$_2$	4 R$_1$=I, R$_2$=H (92)	11 (91)
3.	ICH$_3$	5 R$_1$=CH$_3$, R$_2$=H (82)	12 (90)
4.	(CH$_3$)$_3$SiCl	6 R$_1$=Si(CH$_3$)$_3$, R$_2$=H (78)	-- --
5.	Cl(CH$_2$)$_3$I	7 R$_1$=(CH$_2$)$_3$Cl, R$_2$=H (66)[a]	13 (94)
6.	ClCOOCH$_3$	8 R$_1$=R$_2$=COOCH$_3$ (57)	14 (91)
7.	ClCON(CH$_2$CH$_3$)$_2$	9 R$_1$=R$_2$=CON(CH$_2$CH$_3$)$_2$ (75)	15 (90)

a) yield based on recovered starting material

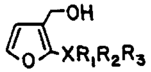
A general experimental procedure follows. A solution of 2 (0.25 g, 1.2 mmol) in DME (5 mL) was cooled to -78°C under argon and treated with n-butyllithium (1.04 mL of 2.5 M in hexane, 2.6 mmol). The solution was stirred at 0°C for 15 minutes and then treated with anhydrous lithium chloride (0.50g, 12 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 5 (82%).

Compound 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 <u>12</u> (90%) after purification[12].

The reaction was not limited to the C-2 substituted t-butyldimethylsilyl furan <u>2</u> 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 <u>2</u> 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(°C)	C-4:C-5 Anion Ratio[b,c]
1.	X=Si, $R_1=R_2=R_3=$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, $R_1=R_2=R_3=$i-Pr	-20	100 : 0
6.	X=Si, $R_1=R_2=R_3=$i-Pr	0	75 : 25
7.	X=C, $R_1=R_2=R_3=$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$_2$O	68 : 32
4.	Et$_2$O / 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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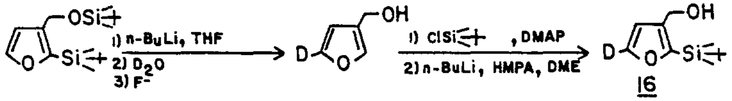
REFERENCES and NOTES

1. Weis, C.D. J. Org. Chem. 1962, 27, 3520. Ansell, M.F.; Caton, M.P.L.; North, P.C. Tetrahedron Lett., 1981, 22, 1727 and references therein.
2. Schultz, A.G.; Motyka, L.A. J. Amer. Chem. Soc., 1982, 104, 5800.
3. Corey, E.J.; Crouse, D.N.; Anderson, J.E. J. Org. Chem., 1975, 40, 2140.
4. Reich, H.J.; Olson, R.E. J. Org. Chem., 1987, 52, 2315.
5. a) Knight, D.W. Tetrahedron Lett., 1979, 20, 469. b) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. ibid, 1983, 24, 5835. Tanis, S.P.; Head, D.B. ibid, 1984, 24, 4451. Katsumura, S.; Hori, K.; Fujiwara, S. ibid, 1985, 26, 4625. Commins, D.L.; Killpack, M.O. J. Org. Chem., 1987, 52, 104.
6. Gschwend, H.W.; Rodriguez, H.R. Organic Reactions, 1979, 26, 1.
7. Meyer, N.; Seebach, D. Angew. Chem., Int. Ed. Engl., 1978, 17, 522.
8. Bures, E.J.; Keay, B.A. Tetrahedron Lett., 1987, 28, in press.
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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