A Facile Preparation of 2,4-Disubstituted Furans

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Abstract: Treatment of 2-(*tert*-butyldimethylsilyl)-3-(triethylsilyloxymethyl)furan with 1.3 equiv. of *n*-BuLi (THF, -40°, 3h), followed by the addition of a variety of electrophiles provided 2,3,5-trisubstituted furans, which upon treatment with tetra-*n*-butylammonium fluoride afforded 2,4-disubstituted furans in moderate to excellent yields.

The preparation of 2,4-disubstituted furans is difficult due to the propensity of the furan ring to add electrophiles or lithiate in the C-2 and/or C-5 position(s). Previous syntheses of furan rings containing a 2,4-disubstituted pattern have involved: a) the synthesis of the furan ring from acyclic precursors;[1] b) electrophilic aromatic substitution of a 2-substituted (to give a 2,3,5-trisubstituted furan)[2a] or 2,5-disubstituted furan ring followed by removal of the C-2 group;[2b] or c) the direct C-5 lithiation of a 2,3-disubstituted furan followed by the removal of the initial C-2 group.[3] Both a bromine atom[2a,3a] and a phenylthio group.[2b,3b,3c] have been successfully removed from the C-2 position of a 2,3,5-trisubstituted furan (i.e. replaced by a hydrogen atom) thereby producing a 2,4-disubstituted furan. We herein report an alternative lithiation route to 2,4-disubstituted furans, employing the *tert*-butyldimethylsilyl group as an easily removable group on the furan ring.
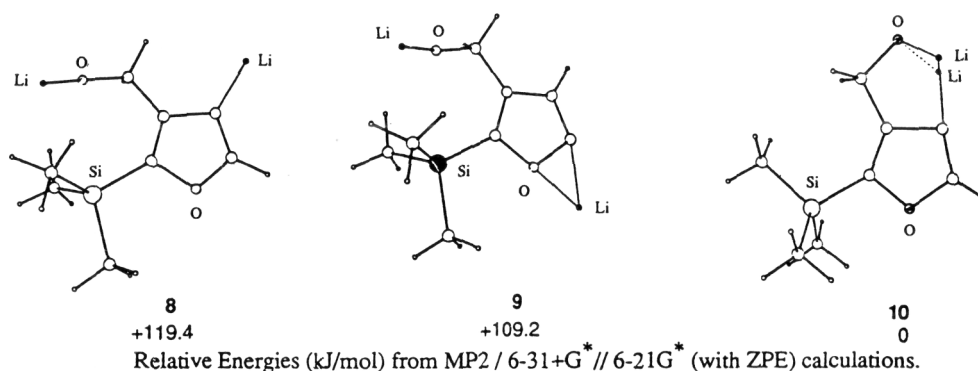
We have recently shown that 2-(*tert*-butyldimethylsilyl)-3-(hydroxymethyl)furan (**1**)[4] can be regiospecifically lithiated at C-4 by treatment with 2.2 equivalents of *n*-butyllithium (DME, 0°C, 1h).[5] Addition of an electrophile provided furan **2**, which was either desilylated[5] (*n*-Bu$_4$NF, THF) to yield furan **3** or treated with NaH in DMF[6] to provide furan **4** (Scheme 1). When the hydroxy group in furan **1** was protected with a
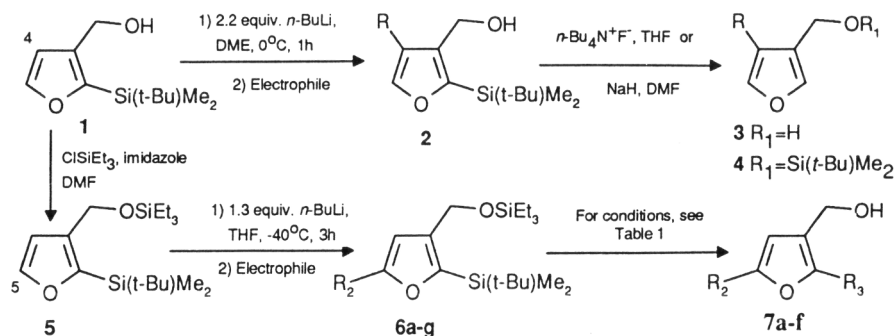
Scheme 1

triethylsilyl group, to provide furan **5**, a regiospecific C-5 lithiation occurred upon treatment with 1.3 equivalents of *n*-butyllithium (THF, -40°C, 3h).[7] The C-5 lithiation was confirmed by the absence of a signal at δ 7.6 in the ^{1}H NMR spectrum of furan **6a** (R_2=D) after quenching the anion of furan **5** with MeOD.

The difference in lithiation regiospecificity between furans **1** and **5** is probably due to two factors. Firstly, the Lewis basicity of the oxygen atom in the triethylsilyloxy group of furan **5** is lower than the Lewis basicity of the oxygen atom in the hydroxymethyl group of furan **1**.[8] Thus, the triethylsilyloxy group is a weaker *ortho*-lithiation director. Secondly, *ab initio* calculations on furans **8-10** (Scheme 2) indicated that furans **8** and **9** are 119.4 and 109.2 kJ/mol higher in energy, respectively, than the bridged dilithio compound **10**.[9] A bridged dilithio compound is not possible in furan **5**, therefore, lithiation occurs at the more acidic C-5 site in furan **5**.[10]

| **8** | **9** | **10** |
| +119.4 | +109.2 | 0 |

Relative Energies (kJ/mol) from MP2 / 6-31+G* // 6-21G* (with ZPE) calculations.

Scheme 2

Table 1: Results from the Lithiation and Subsequent Reactions of Furan **5**.

	Electrophile	Compounds **6a-g** (% Yield)[a]	Conditions	Compounds **7a-f** (% Yield)[a]
1.	MeOD	**6a** R_2=D (95)	AcOH:THF:H$_2$O (8:8:1)	**7a** R_2=D, R_3=Si(t-Bu)Me$_2$ (77)
2.	MeI	**6b** R_2=Me (66)	AcOH:THF:H$_2$O (8:8:1)	**7b** R_2=Me, R_3=Si(t-Bu)Me$_2$ (70)
3.	ICH$_2$CH=CH$_2$	Not isolated[b]	AcOH:THF:H$_2$O (8:8:1)	**7c** R_2=CH$_2$CH=CH$_2$, R_3=Si(t-Bu)Me$_2$ (54)
4.	DMF	**6c** R_2=CHO (88)	AcOH:THF:H$_2$O (8:8:1) *n*-Bu$_4$N$^+$F$^-$, THF	**7d** R_2=CHO, R_3=Si(t-Bu)Me$_2$ (72) **7e** R_2=CHO, R_3=H (83)
5.	ClCONEt$_2$	**6d** R_2=CONEt$_2$ (92)	*n*-Bu$_4$N$^+$F$^-$, THF	**7f** R_2=CONEt$_2$, R_3=H (68)
6.	ClSnBu$_3$	**6e** R_2=SnBu$_3$ (40)	AcOH:THF:H$_2$O (8:8:1)	decomposition[c]
7.	ClCO$_2$Me	**6f** R_2=CO$_2$Me (34)[d]	K$_2$CO$_3$/MeOH[e]	complex mixture

a) All yields are isolated unless otherwise noted.
b) The crude reaction mixture was treated directly with the AcOH:THF:H$_2$O mixture.
c) We found that 2-stannylfurans are very unstable in the presence of various types of acid or *n*-Bu$_4$N$^+$F$^-$.
d) The yield is based on the ^{1}H NMR integration of a mixture of **6f** and 5-(methoxycarbonyl)-3-(methoxycarbonyloxymethyl)-2-(*tert*-butyldimethylsilyl)furan (35%).
e) The above mixture (d) was treated with K$_2$CO$_3$/MeOH.

The C-5 anion of furan **5** was quenched with a variety of reactive electrophiles to provide furans **6a-f** in moderate to excellent yields (Table 1, Scheme 1); however, treatment of the C-5 anion of furan **5** with the unreactive electrophile 3-chloro-1-iodopropane provided the expected 2,3,5-trisubstituted furan **6** in only 30% yield. Therefore, the scope of this reaction appears to be limited to reactive electrophiles. Normal workup involved the addition of a saturated solution of ammonium chloride. Immediate extraction of the mixture with diethyl ether provided **6a-f**; however, if the solution was stirred longer than 15 minutes in the presence of the ammonium chloride, a mixture of furan **6** and the compound resulting from a loss of the triethylsilyl group was obtained. Complete removal of the triethylsilyl group occurred when furans **6** were treated with a mixture of AcOH:THF:H$_2$O (8:8:1); compounds **7a-d** were isolated in good yields. Removal of both silyl groups could be accomplished by treating furans **6** with tetra-n-butylammonium fluoride (THF, r.t., 2h). Thus, furans **6c** and **6d** provided furans **7e** and **7f**, respectively (entries 4 and 5, Table 1).

It would be synthetically useful if the *tert*-butyldimethylsilyl group at C-2 (in furan **6**) could also be used as a protecting group for the C-4 hydroxymethyl group (in **7a-7d**) instead of removing both silyl groups with tetra-n-butyl ammonium fluoride. This idea is illustrated with compound **6b** in Scheme 3. Treatment of furan **6b** with AcOH:THF:H$_2$O provided furan **7b**, which when mixed with NaH in DMF (r.t., 5 min.) provided 2-methyl-4-(*tert*-butyldimethylsilyloxymethyl)furan **11** in 96% yield via a [1,4] C→O silyl rearrangement.[6] The reuse of the *tert*-butyldimethylsilyl group makes our synthetic sequence very economical since the expensive tert-butyldimethylsilyl group has been used as both a blocking group in furan **5** and a protecting group in furan **11**.
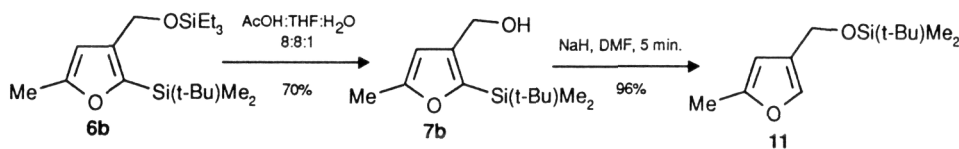
Scheme 3

We have developed a new approach towards the synthesis of 2,4-disubstituted furans in which the silyl groups are easily removed or can be manipulated and used as a protecting group for the resulting C-4 hydroxymethyl group. A full account of the above work and other lithiation studies is currently underway.[5,11]

Typical Experimental

To a mixture of furan **5** (249 mg, 0.761 mmol) in THF (9.4 mL) at -78°C under N$_2$ was added n-butyllithium (1.3 equiv. of 2.5M in hexanes). After stirring the mixture for 3 hours at -40°C, iodomethane (5 equiv.) was added and the mixture was allowed to come to room temperature and stir overnight. The THF was removed *in vacuo* and diethyl ether (5 mL) and saturated ammonium chloride (5 mL) was added to the remaining solid. The ether was separated within 5 minutes, dried (Na$_2$SO$_4$), and removed to leave an oil, which was purified by distillation to provide furan **6b** in 66% yield.[12]

References and Notes

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7. Replacement of the triethylsilyl group in furan **5** by a *tert*-butyldimethylsilyl group also resulted in lithiation at the C-5 position. However, selective cleavage of the Si-O bond in the resulting furan **6** was difficult due to concomitant removal of the C-2 silyl group (Si-C bond). The triethylsilyl group was chosen since it can be selectively removed in the presence of a *tert*-butyldimethylsilyl group, see: Hwu, J.R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599.

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12. All compounds provided analytical and/or spectroscopic data consistent with their structures. Some representative examples are: **Compound 6b**: b.p. 88-94°C/0.04 torr; IR (neat) 1463, 1250 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.38 (s, 6H), 0.65 (q, 6H), 0.91 (s, 9H), 1.0 (t, 9H), 2.28 (s, 3H), 4.53 (s, 2H), 6.04 (s, 1H); ^{13}C NMR (50 Mz, CDCl$_3$) δ -5.7, 4.5, 6.8, 17.4, 26.4, 57.3, 107.0, 137.6, 151.6, 156.1; EIMS m/z 340 (M$^+$), 283 (M$^+$-*t*-Bu); Anal. Calcd for C$_{18}$H$_{36}$O$_2$Si$_2$: C, 63.47; H, 10.65. Found: C, 63.84; H, 10.93. **Compound 7b**: m.p. 50-51°C; IR (neat) 3349, 1253 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.28 (s, 6H), 0.91 (s, 9H), 2.30 (s, 3H), 4.52 (s, 2H), 6.07 (s, 1H); ^{13}C NMR (50 Mz, CDCl$_3$) δ -5.6, 13.7, 17.1, 26.3, 57.3, 106.7, 137.0, 153.0, 156.6; EIMS m/z 169 (M$^+$-*t*-Bu). **Compound 11** b.p. 88-94°C/20 torr; IR (neat) 1465, 1259 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.09 (s, 6H), 0.92 (s, 9H), 2.27 (s, 3H), 4.53 (s, 2H), 5.96 (s, 1H), 7.19 (s, 1H); ^{13}C NMR (50 Mz, CDCl$_3$) δ -5.2, 13.5, 25.9, 30.4, 57.6, 105.6, 126.5, 136.8, 152.6; EIMS m/z 226 (M$^+$). **Compound 6c**: b.p. 88-99°C/0.04 torr; IR (neat) 1688, 1092 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.33 (s, 6H), 0.68 (q, 6H), 0.98 (s, 9H), 1.02 (t, 9H), 4.63 (s, 2H), 7.30 (s, 1H), 9.67 (s, 1H); ^{13}C NMR (50 Mz, CDCl$_3$) δ -6.0, 4.4, 8.8, 15.2, 28.3, 58.7, 120.7, 138.9, 158.8, 161.9, 176.0; EIMS m/z 354 (M$^+$); HRMS calcd for C$_{18}$H$_{34}$O$_3$Si$_2$: 354.2046. Found: 354.2041. **Compound 7d**: b.p. 96-101°C/0.04 torr; IR (neat) 3433, 1678, cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.36 (s, 6H), 0.94 (s, 9H), 1.6 (bs, 1H, -OH), 4.64 (s, 2H), 7.33 (s, 1H), 9.68 (s, 1H); ^{13}C NMR (50 Mz, CDCl$_3$) δ -5.9, 17.3, 26.2, 56.5, 120.7, 136.1, 156.3, 163.2, 178.1; EIMS m/z 240 (M$^+$), 183 (M$^+$-*t*-Bu). **Compound 7e**: b.p. 62-70°C/0.02 torr; IR (neat) 3439, 1693, cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 3.05 (bs, 1H, -OH), 4.57 (s, 2H), 7.24 (s, 1H), 7.63 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (50 Mz, CDCl$_3$) δ 55.7, 120.7, 126.4, 145.3, 153.1, 178.1; EIMS m/z 126 (M$^+$); HRMS calcd for C$_6$H$_6$O$_3$: 126.0317. Found: 126.0308.