

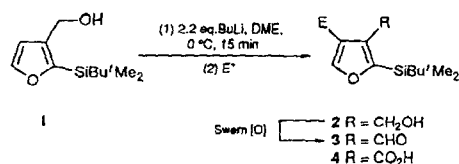
The Regiospecific C-4 Lithiation of 2-(*tert*-Butyldimethylsilyl)-3-furoic Acid

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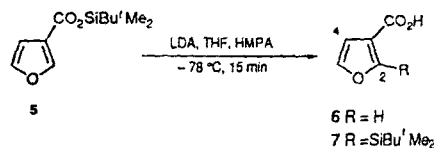
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2-(*tert*-Butyldimethylsilyl)-3-furoic acid **7** was regiospecifically lithiated at the C-4 position when treated with 2.5 equiv. of butyllithium (at -20°C) in either tetrahydrofuran or 1,2-dimethoxyethane; trapping of the dianion with a variety of electrophiles provided 2,3,4-trisubstituted furans in good to excellent yield.

We recently required a preparation of 4-substituted 2-(*tert*-butyldimethylsilyl)-3-furoic acids **4** as intermediates in the synthesis of 3,4-disubstituted furan containing natural products (Scheme 1). Unfortunately the oxidation of a variety of



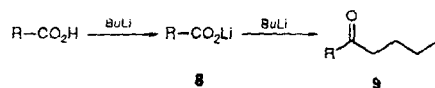
furylaldehydes **3**¹ to the corresponding carboxylic acids **4** failed under a variety of conditions.² Since Knight has reported³ that 3-furoic acid **6** can be regiospecifically lithiated with 2 equiv. of lithium diisopropylamide (LDA) at the C-2 position (exclusively) in THF at -78°C (Scheme 2), we studied the lithiation of



2-(*tert*-butyldimethylsilyl)-3-furoic acid **7** to determine if the carboxylate moiety would direct lithiation to the adjacent C-4 position. We herein report our findings.

2-(*tert*-Butyldimethylsilyl)-3-furoic acid **7** was prepared (72%) as previously described.² The furan **7** when treated with LDA (2.2 equiv.) at -78°C (1 h) in either THF or DME, with or without HMPA, followed by quenching of the dianion with iodomethane afforded no C-4 or C-5 methylated product. Warming of the mixtures to -20°C (1 h) again provided no methylated products.

The absence of methylated products using LDA as the base prompted us to use butyllithium directly on the furan **7**. It is generally recognized that the carboxylic acid moiety is not a good *ortho*-lithiation director when butyllithium is employed as the base.⁴ Usually the second equivalent of butyllithium adds to the initially formed lithium carboxylate **8**, which affords a butyl ketone **9** upon work-up (Scheme 3). Three exceptions to the



above reaction have been reported on heteroatomic systems. Caton *et al.*⁵ and Chadwick *et al.*⁶ have reported that various heterocyclic carboxylic acids can be lithiated with 2 equiv. of butyllithium, while Paltner *et al.* has recently shown⁷ that

similar treatment of phenoxathiin-4-carboxylic acid afforded a C-6 lithiated product.

Treatment of the acid **7** with 2.5 equiv. of butyllithium in THF (-20°C , 1 h) and quenching of the resulting dianion with MeOD provided 4-deuterio-2-(*tert*-butyldimethylsilyl)-3-furoic acid **10** in 90% yield (Table 1). A ¹H NMR spectrum of compound **10** indicated that the C-4 furyl resonance, which was at δ 6.80 in **7**, was absent; the C-5 hydrogen signal appeared at δ 7.63 as a broad singlet. The mass spectrum of the furan **10** confirmed the presence of one deuterium atom.

The dianion of the acid **7** was treated with a variety of electrophiles to provide 4-substituted 2-(*tert*-butyldimethylsilyl)-3-furoic acid (**11**–**17**) in good to excellent yield (Table 1). A few points are noteworthy. The reaction could be performed in either THF or DME and required the addition of HMPA (entries 1–6). Propionaldehyde (entry 7) and iodine (entry 8) did not react with the di-lithium salt of acid **7** (in the presence of HMPA) but reacted smoothly with the dimagnesium salt to provide the corresponding secondary alcohol **16** and the iodo compound **17** respectively.

Some of the products from the above reaction could be desilylated with tetrabutylammonium fluoride (THF, 60°C , 12 h) and the crude reaction mixtures were treated with diazomethane (diethyl ether, 0°C) to provide methyl 4-substituted 3-furoates **18** (Table 1). The 3,4-disubstituted pattern is the more difficult to prepare on furan rings* since furan rings generally lithiate⁴ and add electrophiles at the C-2 and C-5 positions.^{8,9}

To determine if the carboxylic acid moiety at C-3 of the furan rings could be used to direct *ortho*-lithiation with butyllithium alone, we treated 3-furoic acid **6** with 2 equiv. of butyllithium (THF, -20°C , 1 h) and quenched the resulting dianion with iodomethane. 2-Methyl-3-furoic acid **19** and unchanged starting material **6** were formed in 81 and 11% yield respectively; the butyl ketone **20** was neither detected (by ¹H NMR) nor isolated (Scheme 4). Treatment of the furan **19** under the above conditions and quenching of the dianion with MeOD provided the furan **21** (85%) and a small amount of the ketone **22** (8%). Lithiation of benzoic acid **23**, however provided the expected butyl ketone **24** (85%).

These preliminary results indicate that butyllithium can be used directly on some C-3 furoic acids to direct lithiation. The increased acidity of the C-2 furan hydrogen¹⁰ in **6** and γ hydrogens¹¹ in **19** relative to the C-2 hydrogens in benzoic acid **23** may be responsible for the above results.

The successful C-4 lithiation of the furan **7** may be due to the presence of the bulky C-2 *tert*-butyldimethylsilyl group.¹² Molecular modelling studies† indicated that the lowest energy

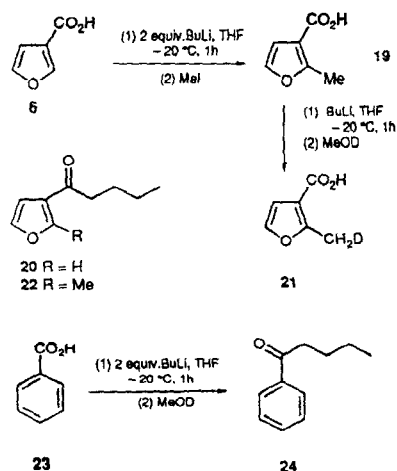
* A Diels-Alder/retro Diels-Alder sequence has been employed to prepare 3,4-disubstituted furans having carboxylic acid or aldehyde groups as one of the substituents, see ref. 9.

† The modelling program PCMODEL (version 4D, Serena Software) was used for the minimization.

Table 1 Preparation of 4-substituted 2-silyl-3-furoic acids

Entry	Electrophile	Solvent	Additive	Product (% Yield) ^a	Product (% Yield) ^a
1	MeOD	THF	—	10 E = D (90)	E = D (86)
2	MeI	DME	HMPA	11 E = Me (88)	E = Me (90)
3	DMF	DME	HMPA	12 E = CHO (87)	—
4	Me ₃ SiCl	DME	HMPA	13 E = SiMe ₃ (86)	—
5	Bu ₃ SnCl	THF	HMPA	14 E = SnBu ₃ (86)	—
6	CO ₂	THF	HMPA	15 E = CO ₂ H (69)	E = CO ₂ Me (40)
7	CH ₃ CH ₂ CHO	THF	MgBr ₂	16 E = CH(OH)Et (52)	E = CH(OH)Et (31)
8	I ₂	THF	MgBr ₂	17 E = I (71)	E = I (87)

^a Isolated yields.



Scheme 4

conformation of the lithium carboxylate of 7 has the carboxylate group coplanar with the furan ring. In addition, one of the oxygen atoms of the carboxylate bisects the two methyl groups attached to the silicon atom. Thus, attack by the second equivalent of butyllithium on the lithium carboxylate group may be hindered by the methyl groups, thereby allowing the lithium carboxylate group to direct lithiation to C-4 of furan 7. Further studies are in progress.

We have, therefore, shown that 2-(*tert*-butyldimethylsilyl)-3-furoic acid 7 can be regioselectively lithiated at C-4 with 2.5 equiv. of butyllithium and the resulting dianion trapped with a variety of electrophiles to provide 4-substituted 2-silylated 3-furoic acids in excellent yields.*

Experimental

A solution of the furan 7 (1 mmol) in THF (5 ml) under argon was cooled to -78°C and treated with butyllithium (2.5 mmol). The solution was stirred at -20°C for 1 h and then treated with

HMPA (2.5 mmol) (or MgBr₂; 5 mmol). The mixture was stirred for a further 1 h after which the electrophile (1.2 mmol) was added and the solution stirred at 0°C for 6 h. The solution was quenched with water and acidified with 10% HCl. An ethyl acetate extraction, drying (Na₂SO₄) and removal of the solvent under reduced pressure followed by chromatography on a silica gel column gave the 4-substituted 2-silylated 3-furoic acid.

Acknowledgements

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* All compounds provided analytical and/or spectroscopic data consistent with their structures.