

Lithiation of 3,4-Bis(tri-*n*-butylstannyl)furan: Regiospecific Synthesis of Unsymmetrical 3,4-Disubstituted Furan[†]

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3-(Tri-*n*-butylstannyl)-4-lithiofuran **2**, obtained through tin–lithium exchange from 3,4-bis(tri-*n*-butylstannyl)furan **1**, reacts regiospecifically with various electrophiles to give monosubstituted stannylfurans, which are converted into unsymmetrical 3,4-disubstituted furans utilising Stille's palladium-catalysed coupling reactions.

Polysubstituted furans, which serve as important starting materials and intermediates in natural and non-natural products syntheses, have received wide interest and have accordingly been studied extensively.¹ However, the synthesis of 3,4-disubstituted furans still remains a formidable challenge since direct substitution at C-3 and/or C-4 is not trivial.¹ Several procedures have been devised in order to overcome this difficulty,² but a concise and general route is still lacking. In a recent communication, we reported the synthesis of 3,4-bis(tri-*n*-butylstannyl)furan **1** and its conversion into symmetrical as well as unsymmetrical 3,4-disubstituted furans.¹ In this communication, we report the regiospecific tin–lithium exchange of **1**, the alkylation of the resulting lithium salt and displacement of the remaining stannyl group



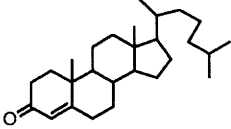
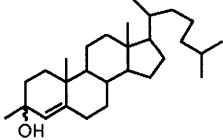
with electrophiles *via* the Stille procedure.³ This pathway represents a facile entry to various unsymmetrical 3,4-disubstituted furans.

Although arylstannanes are known to undergo tin–lithium exchange with alkyllithium, such a transformation has seldom been applied to organic synthesis.⁴ Inspired by the work of Fleming and Taddei,⁵ we treated **1** with various amounts of *n*-butyllithium and found that approximately 2 equiv. of *n*-butyllithium were needed to achieve complete exchange of one stannyl group, generating **2**.[‡] Smaller amounts of *n*-butyllithium merely led to incomplete exchange, while

[†] 3,4-Disubstituted furans: Part 3. Part 2: Y. Yang and H. N. C. Wong, *J. Chem. Soc., Chem. Commun.*, 1992, 656.

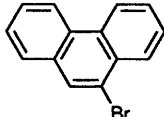
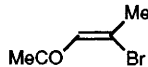

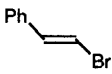
[‡] The reaction was monitored by hydrolysing small amounts of the resulting solution and checking on reverse-phase TLC, which separated **1** and 3-stannylfuran. When **1** disappeared, lithium–tin exchange was complete.

Table 1 Lithiation of **1** and reaction of lithiofuran **2** with electrophiles^a

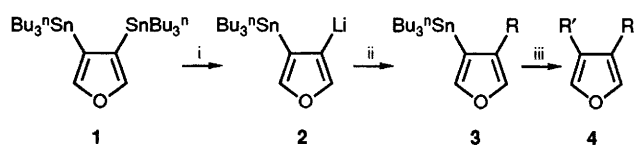
Entry	Electrophile	R	Stannylfuran 3	Yield (%) ^b
1	Me ₂ SO ₄	Me	a	65
2	Me ₂ SO ₄	Me	a	36 ^c
3	HCONMe ₂	CHO	b	58 ^c
4	HCONMe ₂	CHO	b	69 ^d
5	HCONMe ₂	CHO	b	86
6	EtCONMe ₂	COEt	c	63
7	Me ₂ CO	C(OH)Me ₂	d	60
8	PhCHO	CH(OH)Ph	e	75
9	Ph ₂ CO	C(OH)Ph ₂	f	79
10	MeI	Me	a	28
11	H ₂ CO	CH ₂ OH	g	19
12			h	63
13			i	44

^a Typical procedure: synthesis of **3b**: to a solution of **1** (0.4 mmol) in THF (5 ml) at -78°C was added dropwise n-butyllithium (0.88 mmol); the resulting solution was stirred at -78°C for 0.5 h before a mixture of DMF (0.9 mmol) and DMPU (0.88 mmol) was added. After 1 h at -78°C , the solution was warmed to room temp., quenched with saturated NH₄Cl (5 ml), extracted with diethyl ether (3 \times 20 ml), dried (MgSO₄) and purified by chromatography on neutral alumina. ^b Isolated yields. ^c Electrophile added alone. ^d TMEDA added together with equal amount of n-butyllithium: DMF = *N,N*-dimethylformamide, TMEDA = *N,N,N',N'*-tetramethylethylenediamine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, THF = tetrahydrofuran.

Table 2 Pd-catalysed coupling of monosubstituted stannylfurans **3** with electrophiles

Entry	Stannylfurans 3 ; R	RX (X = Br)	Catalyst (5 mol%)	Conditions ^a T / $^{\circ}\text{C}$; t / h	Product yield ^b (%)
1	a ; Me		Pd(PPh ₃) ₄	80; 8	4a (35)
2	d ; C(OH)Me ₂		[(C ₃ H ₅)PdCl] ₂	r.t.; 24	4b (66)
3	e ; CH(OH)Ph	PhCH ₂ Br	Pd(MeCN) ₂ Cl ₂	60; 2	4c (70)
4	f ; C(OH)Ph ₂	<i>p</i> -MeCOC ₆ H ₄ Br	Pd(PPh ₃) ₄	75; 24	4d (61)
5 ^c	h ; 		[(C ₃ H ₅)PdCl] ₂	r.t.; 24	4e (76)

^a R.t. = room temp. ^b Isolated yields. ^c The solvents used were DMF:hexamethylphosphoramide 10:1.



Scheme 1 Reagents and conditions: i, BuⁿLi (2.2 equiv.), THF, -78°C ; ii, DMPU, electrophile; iii, R'X, [Pd], DMF

larger amounts (up to 4 equiv.) of n-butyllithium gave no sign of exchange with the second stannyl group. It came as no surprise since this kind of difficulty in connection with the simultaneous removal of two stannyl groups has been well-documented in bis-stannylalkenes⁶ as well as bis-stannylarenes.⁷ Such a seemingly unfavourable restriction, however, led to the prospect of unsymmetrical 3,4-disubstituted furan synthesis. The regioselective reactions of **2** are depicted by

examples as outlined in Table 1. § As can be seen, yields were unsatisfactory (entries 2 and 3) in the absence of TMEDA, but were improved significantly in its presence (entry 4). The best results were obtained when DMPU was added together with the electrophile. With α,β -unsaturated ketones, only 1,2-addition was observed (entries 12 and 13). To obtain good yields, reactive electrophiles such as dimethyl sulfate and carbonyl compounds should be used. With less reactive electrophiles and formaldehyde, yields were inferior (entries 10 and 11).

The mono-substituted stannylfurans thus formed were then allowed to undergo Stille's palladium-catalysed coupling

reactions to give unsymmetrical 3,4-disubstituted furans.¹ Some examples are given in Table 2. §

In conclusion, furans with diverse substituents, which are otherwise difficult to synthesise, were conveniently prepared by utilising this method.

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§ *Selected spectroscopic data*: Compound **3a**: ¹H NMR (CDCl₃) δ 0.89 (m, 9H), 1.02 (m, 6H), 1.32 (m, 6H), 1.50 (m, 6H), 2.02 (d, *J* 1.0 Hz, 1H), 7.11 (d, *J* 1.0 Hz, 1H), 7.29 (d, *J* 1.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 9.76, 11.53, 13.57, 27.25, 29.20, 117.16, 124.80, 139.25, 147.55. **3b**: ¹H NMR (CDCl₃) δ 0.79 (m, 9H), 1.00 (m, 6H), 1.20 (m, 6H), 1.40 (m, 6H), 7.14 (d, *J* 1.0 Hz, 1H), 8.08 (d, *J* 1.0 Hz, 1H), 9.89 (s, 1H); ¹³C NMR (CDCl₃): δ 10.27, 13.49, 27.12, 29.05, 113.43, 133.75, 149.26, 152.60, 185.11. **4a**: light yellow leaflets (MeOH); m.p. 119–121 °C; ¹H NMR (CDCl₃) δ 1.87 (d, *J* 1.0 Hz, 3H), 7.40 (t, *J* 1.0 Hz, 1H), 7.53–7.69 (m, 6H), 7.87 (m, 2H), 8.73 (m, 2H); ¹³C NMR (CDCl₃) δ 8.53, 122.58, 122.86, 125.91, 126.61, 126.78, 126.89, 128.54, 139.83, 140.96. **4b**: yellow solid; m.p. 65–67 °C; ¹H NMR (CDCl₃) δ 1.56 (s, 6H), 2.22 (s, 3H), 2.45 (d, *J* 1.1 Hz, 3H), 6.74 (d, *J* 1.1 Hz, 1H), 7.33 (d, *J* 1.8 Hz, 1H), 7.38 (d, *J* 1.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 13.48, 21.04, 30.74, 31.90, 68.69, 127.51, 128.64, 131.67, 139.87, 142.04, 146.92, 198.80.