## Regionelective Lithiations of Di(2-thianyl)methane: A Clean Kinetic and Thermodynamic Control in Lithiation

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**Abstract:** Di(2-thienyl)methane is regioselectively lithiated at either 5-position of the thienyl group or the central methylene carbon depending on base, solvent, additive, and temperature; the results give a novel example of kinetic and thermo-dynamic control in lithiation and explain the previous controversial results.

Although the lithiation of thiophene and its derivatives has been extensively studied and applied to organic synthesis,<sup>1,2</sup> the lithiation (or metalation in general) of di(2-thienyl)methane 1 seems to have remained controversial. The lithiation of 1 with alkyllithium has been reported to take place selectively at 5-position of the thienyl group to give thienyllithium 2 (C5-metalation).<sup>3</sup> A recent report<sup>4</sup>, however, briefly noted a failure of formylation through 2. On the other hand, treatment of 1 with potassium amide and diethyl carbonate in liquid ammonia effected carboethoxylation, though in poor yield, at the central methylene carbon.<sup>5</sup> This apparently indicates the intermediate formation of dithienylmethyl anion 3 (C $\alpha$ -metalation). Thus, governing factors on these results would be questioned. Here we report the regioselective C5-lithiation and C $\alpha$ -lithiation of 1, which provides a novel example of clean kinetic and thermodynamic control of lithiation leading to a good understanding of the controversial results.



The lithiation of 1 with n-butyllithium in ether or THF below 0 °C indeed selectively generated 2, as reported<sup>3</sup>, by giving the alcohol 4 after quenching with benzaldehyde (Table 1, Entry 1 and 2).

However, in view of stronger stabilizing effects of 2-thienyl group than phenyl group on not only carbocations<sup>6</sup> but also carbanions<sup>7</sup>, the Ca-protons of 1 would be more acidic than those of diphenylmethane (pKa =  $32.2^8$ ) and accordingly even more acidic than dimethylsulfoxide (DMSO, pKa =  $35^8$ ). On the other hand, the C5-protons must be less acidic than DMSO, even though they receive the heteroatom assistance of

the adjacent sulfur atom for metalation.<sup>9</sup> Therefore, methylsulfinylmethyl (dimsyl) anion should effect metalation only at  $C\alpha$  of 1 to afford 3.

In fact, treatment of 1 with sodium hydride or n-butyllithium in DMSO-THF (1/1 v/v) cleanly generated  $3^{10}$  which shows <sup>1</sup>H and <sup>13</sup>C NMR signals of Ca at  $\delta$  5.27 and 72.84 (Na-salt), and quenching of the solutions with benzaldehyde afforded the alcohol 5d in good yield (Entry 4). In deuterated DMSO and sodium hydride, the <sup>1</sup>H NMR signal of the Ca-proton soon disappeared (within 15 min at room temperature) by exchange with deuterium, whereas the C5-protons slowly disappeared over a few days in agreement with the acidity considerations.

Lithium diisopropylamide (LDA) also effected the selective  $C\alpha$ -lithiation in THF in spite of possible direction to the C5-lithiation by the sulfur atom (Entry 5).

Addition of 1.5 equivalents of tetramethylethylenediamine (TMEDA) to n-BuLi-THF showed a remarkable temperature dependence of the selectivity: the C5-lithiation at -60 °C but the C $\alpha$ -lithiation at 0 °C (Entry 6 and 7). The more TMEDA is added, the more the C $\alpha$ -lithiation is favored. Accordingly, the C $\alpha$ -lithiation was resulted even at -60 °C in a 1:1 mixture of THF-TMEDA (Entry 8). Addition of hexamethylphosphortriamide (HMPA) also favored the C $\alpha$ -lithiation (Entry 9).



Entry	Base	Solvent	Temp. (°C)	Products, yield % <sup>C</sup>	
	Dasc	3017611		4	5 d
1	BuLi	Ether	0	67	0
2	BuLi	THF	0	70	0
3	<b>BuL</b> i	THF	20 <sup>d</sup>	30	56
4	BuLi	THF - $Me_2SO(1:1)$	0	0	86
5	LDA	THF	0	0	96
6	BuLi	THF - TMEDA(1.5 eq)	-60	0	60
7	BuLi	THF - TMEDA(1.5 eq)	0	62	0
8	BuLi	THF - TMEDA(1:1)	-60	0	79
9	BuLi	THF - HMPA (1:1)	0	0	44

Table 1. Selective monolithiation<sup>a</sup> and quenching<sup>b</sup> of 1

<sup>a</sup> Lithiations were performed for 30 min using 1.2 equivalent of bases unless otherwise noted. <sup>b</sup> Benzaldehyde was used as a quencher. <sup>c</sup> Yields after purification by chromatography on silica gel. <sup>d</sup> Lithiation was performed for 2h.



Scheme 1 shows a rationalization of these results. The C5-lithiation forming 2 in ether and THF is apparently kinetically controlled by assistance of the sulfur atom. Dimsyllithium is strong enough for the Ca-lithiation but not for the C5-lithiation. When LDA is used, the liberated diisopropylamine, of which acidity is comparable to the acidity of the C5-protons<sup>9,11</sup>, can mediate smooth equilibrium between 2 and 3 in favor of thermodynamically more stable 3. In the presence of TMEDA and HMPA, we postulate the intermediacy of the dianion 6 for the transformation of 2 to 3. High solvating ability of these additives should form the solvent-separated ion pairs and hence increase the reactivity of 2 with enhanced free ion nature. Disproportionation between two molecules of 2 would generate 6 and 1 which in turn rapidly give two molecules of more stable 3. THF can solvate to lithium ion better than ether, and actually THF solution of 2 slowly gave rise to 3 at 20 °C (Entry 3).

The dianion 6 must be less stable than the other possible dianion 7 due to severer electronic repulsion. The action of excess n-butyllithium on 1 in THF had been reported<sup>3</sup> and was confirmed here to give 7. The dianion 7 was still the product in the presence of 3 equivalents of TMEDA at 0  $^{\circ}$ C, whereas the monoanion 3 remained mostly unchanged in 1:1 THF-TMEDA as judged from quenching experiments.

The anion 3 is less reactive than the anion 2 toward electrophiles (Table 2): it reacted with methyl iodide, carbon dioxide, and aldehydes, but did not react with ketones and dimethylformamide regenerating 1 upon work-up (the reactions can be monitored by disappearance of red color of 3).

Therefore, choice of proper conditions for the lithiation and proper electrophiles for next quenching is important for the satisfactory selective functionalization of 1.

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Entry	Electrophile	Product 5 <sup>b</sup> E	Yield %
	CUL COOD		
1	CH <sub>3</sub> COOD	58 D(>98%)	91%
2	CH3I	5b CH <sub>3</sub>	96%
3	CO <sub>2</sub>	5c COOH	89%
4	PhCHO	5d CH(OH)Ph	86%
5	DMF	recovery	75%
6	CH <sub>3</sub> COCH <sub>3</sub>	recovery	86%
7	PhCOPh	recovery	90%

Table 2. Reactions of 3 with electrophiles<sup>4</sup>

<sup>a</sup> Lithiation was performed in THF-DMSO (1 : 1) at 0 °C for 30 min using n-BuLi.

<sup>b</sup> Correct mass and NMR spectral data were obtained for **5a-d**.<sup>c</sup>D-incorporation.

## **References and Notes**

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- 9. Thiophene is lithiated up to about 50% by LDA,<sup>2</sup> and diisopropylamine has the acidity of pKa =  $35.7.^{11}$  Therefore, the acidity of the C5-protons of 1 is estimated to be about 36 (pKa).
- 10. <sup>1</sup>H NMR:  $\delta$  (Na-salt in DMSO-d<sub>6</sub>) 5.27 (1H, s), 5.46 (2H, dd, J = 3.6 Hz), 5.64 (2H, dd, J = 4.6 Hz), 6.46 (2H, dd, J = 4.6, 3.6 Hz); (Li-salt in THF-d<sub>8</sub>) 5.21 (1H, s), 5.46 (2H, dd, J = 3.6 Hz), 5.46 (2H, dd, J = 4.6 Hz), 6.35 (2H, dd, J = 4.6, 3.6 Hz) <sup>13</sup>C NMR:  $\delta$  (Na-salt) 72.84 (C $\alpha$ ), 97.78 (C5), 97.94 (C3), 127.04 (C4), 149.23 (C2); (Li-salt) 72.74, 98.25, 100.70, 127.40, 151.60.
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