Aromatic Ring-Opening of 2-Fluorobenzothiophenes by Alkyllithiums

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Abstract: Diphenylacetylenes are obtained when alkyllithium reagents are added to 3-aryl-2-fluorobenzothiophenes at low temperature. The aromatic ring-opening mechanism involves a nucleophilic addition of the alkyllithium to the sulfur atom of the thiophene. The resulting 2,2-diaryl-1-fluorovinyl anion subsequently undergoes a Fritsch–Buttenburg–Wiechell rearrangement to afford the diphenylacetylene.

Key words: ring-opening, Fritsch–Buttenberg–Wiechell rearrangements, benzothiophenes, alkyllithium reagents, addition to sulfur

Thiophenes usually react with organolithium reagents to yield 2-lithiothiophenes, which are quite stable and can react with various electrophiles. However, 3-lithio-thiophenes are obtained from deprotonation of a 2,5-di-substituted thiophene (with BuLi or LDA) or by halogenmetal exchange between 3-bromothiophenes and BuLi. 3-Lithiothiophenes are generally stable at -78 °C, where they can react with electrophiles, but they rearrange to acetylenic thiolates **1** at 0 °C (Equation 1).¹



Equation 1

We have recently discovered that organolithium reagents can also undergo nucleophilic addition onto the sulfur atom of some thiophenes, which lead to their cleavage at low temperature.² Two examples of this unexpected reaction are given in Equation 2 and Equation 3. In general, these nucleophilic additions are only observed with chlorothiophenes fused to another aromatic ring, with only one known exception: addition of butyl- or phenyllithium to 3,4-dichloro-2,5-dimethoxythiophene affords dibutyl or diphenyl sulfide at room temperature.³ Herein, we describe the effect of replacing the chlorine with other electron withdrawing substituents on the aromatic ringopening of thiophenes.

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We initially prepared 2-(trifluoromethyl)-3-phenylbenzothiophene (**6**, Figure 1),⁴ but this substrate was inert toward butyllithium. We then discovered that the fluoro analog 2-fluoro-3-phenylbenzothiophene (**7a**) reacted with butyllithium to yield 1-(butylthio)-2-(phenylethynyl)benzene **5a**⁵ (Table 1).

Diphenylacetylene 5a has been synthesized previously from two closely related reactions. It was obtained first from the reaction of BuLi with 3-bromo-2-phenylbenzothiophene, via the rearrangement of a 3-lithiobenzothiophene intermediate to an acetylenic thiophenolate (as in Equation 1), and its subsequent reaction with the butyl bromide generated in situ.^{1a} The acetylene 5a was also obtained via a nucleophilic attack with BuLi onto the sulfur atom of 3-chloro-2-phenylbenzothiophene 4 at -78 °C (Equation 3).² However, the formation of 5a from 2-fluorobenzothiophene 7a cannot be explained using the mechanisms operating in these two processes.



Scheme 1

 Table 1
 Reactions of Organolithium Reagents with 2-Fluoro-3-phenylbenzothiophenes¹⁵

×	Ar S	1) 1.3 equiv RLi, THF 2) NH_4CI	Ar				
	7		5				
SM	Х	Ar	RLi	Temp (°C)	Product 5		Recovered SM
No						Yield (%)	Yield (%)
7a	Н	Ph	BuLi ^a	-78, 4 h	5a	49	38
7a	Н	Ph	BuLi ^b	-40, 1 h	5a	66	Trace
7a	Н	Ph	<i>t</i> -BuLi ^a	-72, 1 h	5b	68	
7a	Н	Ph	s-BuLi ^b	-78 to r.t.		0	100
7b	Н	4-(MeO)C ₆ H ₄	BuLi	-78 to 0	5c	48 ^c	Trace
7b	Н	4-(MeO)C ₆ H ₄	t-BuLi	-78 to 0	5d	43	18
7b	Н	4-(MeO)C ₆ H ₄	s-BuLi	-78 to 0	5e	51	32
7c	Cl	Ph	BuLi	-78 to 0	5f	17	
7c	Cl	Ph	t-BuLi	-78 to 0	5g	25	Trace
7c	Cl	Ph	s-BuLi	-78 to 0	5h	44	26
7a–c	H or Cl	Ph or 4-(MeO)C ₆ H ₄	MeLi or PhLi	-78 to 0		0-5 ^d	20-80
7d	Н	$2,4-Cl_2C_6H_3$	All RLi above	-78 to 0		0	Major product (HPLC)

^a 2 Equiv.

^b 5 Equiv.

 $^{\rm c}$ 24% Yield of 2-butyl-3-(4-methoxyphenyl) benzothiophene (10a).

^d 0–29% Yields of 2-methyl- or 2-phenyl-3-arylbenzothiophenes 10.

Our proposed mechanism for this new reaction⁶ is summarized in Scheme 1. The first and rate-limiting step⁷ involves a nucleophilic addition of the organometallic reagent onto the sulfur atom of benzothiophene 7 to generate the intermediate 2,2-diaryl-1-fluorovinyllithium 8. As the second step, intermediate 8 undergoes a Fritsch-Buttenberg–Wiechell (FBW) rearrangement,⁸ during which the migration of the aryl group occurs *trans* to the

halogen,⁹ either through a carbene or a carbenoid-like mechanism, to yield the diphenylacetylene **5**.

In order to study the scope and limitations of this novel diphenylacetylene synthesis, the four fluorinated benzo-thiophenes **7a–d**, bearing electron-withdrawing or donating substituents, were prepared as summarized in Scheme 2. The key steps were a Suzuki–Miyaura coupling reaction between triflate **8a** or 3-bromobenzothiophene **8b**¹⁰ and a phenylboronic acid in the



Scheme 2

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presence of tetrakis(triphenylphosphine) palladium(0)¹¹ to prepare the intermediates **9a–d**, which were then deprotonated in position 2 with butyllithium and fluorinated with *N*-fluorobenzenesulfonimide¹² to give the 2-fluorobenzothiophenes **7a–d** in fair to excellent yields. The triflate **8a** was obtained from an intramolecular Friedel–Craft acylation of [(4-chlorophenyl)thio]acetyl chloride, prepared in situ from the acid and PCl₃,¹³ followed by its reaction with trifluoromethanesulfonic anhydride.¹⁴

As can be seen from Table 1, the formation of diphenylacetylenes from 2-fluoro-3-phenylbenzothiophene is not general and the yields vary with the substitution pattern of the benzothiophene and the nature of the organolithium reagent. With the exception of methyllithium, alkyllithium reagents usually gave diphenylacetylenes in moderate to good yield. With methyllithium and phenyllithium, the major products observed, other than the unreacted starting material (SM), are products 10, arising from nucleophilic aromatic substitution (S_NAr) of the fluoride by the organometallic reagent. Addition of a co-solvent such as DMPU, or a complexing agent such as TMEDA, had no effect on the reactivity of methyllithium. Finally, with 2fluoro-(2,4-dichlorophenyl)benzothiophene 7d, the starting material was mostly recovered unchanged in many reactions, along with small amounts of unidentified compounds, which did not contain any alkyl group coming from the organometallic reagent. It seems that the presence of EWG on the 3-aryl substituent greatly decreases the speed of the alkyllithium addition onto the sulfur atom of the thiophene.

This diphenylacetylene formation proceeds when THF is used as solvent. No ring-opening of benzothiophenes is observed in diethyl ether, even in the presence of TMEDA or with a large excess of BuLi at room temperature. The temperature of the reaction and quantity of alkyllithium reagent are also important. For example, when **7a** was reacted with an excess of alkyllithium at -20 °C, the side product **11**, arising from addition of a second molecule of butyllithium across the triple bond of the diphenyl-acetylene **5a**,¹⁶ was also isolated (12% yield).



Figure 1

In order to compare the behavior of 2-fluorobenzothiophenes with their 2-chloro analogs toward such organolithium addition, 2-chloro-3-phenylbenzothiophene $(12)^{17}$ was treated with butyllithium under similar conditions. In this particular reaction,¹⁸ the diphenylacetylene **5a** was obtained only as a minor product (max. 10% yield). The major product, 3-phenylbenzothiophene (**13**, 84% yield by ¹H NMR of the crude reaction mixture), was formed via a chlorine-metal exchange, showing that 2-chlorobenzothiophenes are not good substrates for the thiophene ring-opening reaction. The low yield of diphenylacetylene **5a** isolated in this example was strikingly different from what was observed in Equation 2, where the 2-chlorothieno[3,2-*d*]thiazole (**2**) was found to yield exclusively the ring-opened product **3**, and where the chlorine-metal exchange was absent.² Thienothiazoles are evidently more susceptible to nucleophilic organolithium addition than their benzothiophene analogs.

In conclusion, we have reported here new examples of a surprising ring-opening of thiophenes in which alkyllithium reagents add to the sulfur atom of the thiophene and in which diphenylacetylenes are produced after a FBW rearrangement of the intermediate carbenoids.

General Experimental Procedure¹⁵

Reaction of 2-Fluoro-3-arylbenzothiophenes 7 with Organolithium Reagents:

Compound 7 (100 mg) was dissolved in 5 mL of dry THF and cooled to -78 °C under a nitrogen atmosphere. Then, 1.2 equiv of organolithium reagent was added and the reaction mixture was slowly warmed up to 0 °C over 40 min. A sat. solution of NH₄Cl was added and the products of the reaction were extracted into EtOAc and dried over Na₂SO₄. The mixture was analyzed by HPLC (NovaPak column, gradient 20–95% MeCN–NH₄OAc buffer (2 g/L containing 10% MeOH). Purification of the products was performed either by flash chromatography on silica or normal phase HPLC (Luna 10 µm silica column, 250 × 10 mm).

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- (4) Lithiation of **9a** with BuLi in THF at -78 °C, in the presence of TMEDA, followed by reaction with iodine,¹⁹ yielded quantitatively 2-iodo-3-phenylbenzothiophene. Trifluoromethylation of this iodide (2.0 g) was then performed in 59% yield with CF₃I (2.3 mL) and copper (5.0 g) in pyridine (13 ml) at 130 °C for 24 h. See: Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *42*, 4071; for a related procedure.
- (5) The structure of the diphenylacetylene **5a** was confirmed by its preparation via an alternative synthetic route. *o*-Bromothiophenol was butylated with butyl iodide in the presence of NaH in DMF. Phenylacetylene was converted to its lithium salt and treated with *B*-MeO-9-BBN in situ to form a

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tetrahedral borate complex, which was reacted with 1-bromo-2-(butylthio)benzene in the presence of $Pd(0)^{20}$ to yield **5a**.

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- (15) All new compounds gave satisfactory analytical and spectroscopic data. Selected data: **1-**(*tert*-**Butylthio**)-**2-**[(**4-methoxyphenyl**)**ethynyl]benzene** (**5d**): ¹H NMR (500 MHz, acetone): δ = 7.67 (d, 1 H, *J* = 7.7 Hz), 7.64 (dd, 1 H, *J* = 1.0, 7.6 Hz), 7.54 (d, 2 H, *J* = 8.8 Hz), 7.46–7.44 (m, 1 H), 7.41–7.37 (m, 1 H), 7.01 (d, 2 H, *J* = 8.8 Hz), 3.86 (s, 3 H), 1.37 (s, 9 H). ¹³C NMR (126 MHz, acetone): δ = 160.49, 139.14, 135.01, 133.26, 133.00, 131.43, 129.35, 128.33, 115.83, 114.65, 93.56, 88.61, 55.25, 47.74, 31.04. IR (neat): 2216 cm⁻¹. HRMS (FAB, glycerol): *m/z* calcd for C₁₉H₂₀OS [M⁺]: 296.1234; found: 296.1236. Anal. Calcd for C₁₉H₂₀OS: C, 76.98; H, 6.80; S, 10.82. Found: C, 76.98; H, 7.04; S, 9.97.

(5g): ¹H NMR (500 MHz, acetone): δ = 7.68 (m, 2 H), 7.63– 7.61 (m, 2 H), 7.48–7.44 (m, 4 H), 1.38 (s, 9 H). ¹³C NMR $(126 \text{ MHz}, \text{ acetone}): \delta = 140.44, 134.93, 134.19, 132.65,$ 132.55, 131.90, 129.36, 129.09, 128.83, 123.31, 94.60, 88.54, 48.24, 30.97. IR (neat): 2220 cm⁻¹. HRMS (FAB, glycerol): *m/z* calcd for C₁₈H₁₇ClS [M⁺]: 300.0740; found: 300.0738. Anal. Calcd for $C_{18}H_{17}ClS: C$, 71.86; H, 5.70; S, 10.66. Found: C, 71.93; H, 5.90; S, 10.27. 2-Fluoro-3-(4-methoxyphenyl)benzothiophene (7b): ¹H NMR (500 MHz, acetone): δ = 7.91–7.87 (m, 1 H), 7.72– 7.68 (m, 1 H), 7.52 (d, 2 H, J = 8.1 Hz), 7.46–7.40 (m, 2 H), 7.14–7.12 (m, 2 H), 3.89 (s, 3 H). ¹³C NMR (126 MHz, acetone): δ = 160.00, 159.31 (d, J = 289 Hz), 136.49 (d, *J* = 3.9 Hz), 131.02 (d, *J* = 2.6 Hz), 130.89, 125.80, 125.30 (d, J = 4.6 Hz), 123.35, 123.28, 122.87 (d, J = 6.0 Hz),117.13 (d, J = 7.3 Hz), 114.74, 55.18. MS (+APCI): m/e 258.0 [M⁺]. Anal. Calcd for C₁₅H₁₁FOS: C, 69.75; H, 4.29; S, 12.41. Found: C, 69.84; H, 4.34; S, 12.28. 5-Chloro-2-fluoro-3-phenylbenzothiophene (7c): ¹H NMR (500 MHz, acetone): $\delta = 7.99$ (d, 1 H, J = 8.6 Hz), 7.67 (d, 1 H, J = 2.0 Hz), 7.61 (m, 4 H), 7.52 (m, 1 H), 7.46 (dd, 1 H, J = 2.0, 8.6 Hz). ¹³C NMR (126 MHz, acetone): $\delta =$ 161.58 (d, J = 291 Hz), 138.02 (d, J = 4.3 Hz), 132.28, 131.06, 130.11, 129.92, 129.82 (d, J = 2.9 Hz), 129.24, 126.08 (d, J = 4.1 Hz), 125.56, 122.71 (d, J = 6.2 Hz), 117.71 (d, J = 8.0 Hz). MS (+APCI): m/e 262.0 [M⁺], 264.0. Anal. Calcd for C₁₄H₈CIFS: C, 64.00; H, 3.07. Found: C, 64.45; H, 3.00.

1-(tert-Butylthio)-4-chloro-2-(phenylethynyl)benzene

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