Aromatic Ring Opening of Fused Thiophenes via Organolithium Addition to Sulfur

B. Hill, M. De Vleeschauwer, K. Houde, M. Belley*

Merck Frosst Centre for Therapeutic Research, Department of Medicinal Chemistry, 16711 Route Transcanadienne, Kirkland, Québec, H9H 3L1, Canada

Fax (514) 428-4936; E-Mail: belley@merck.com

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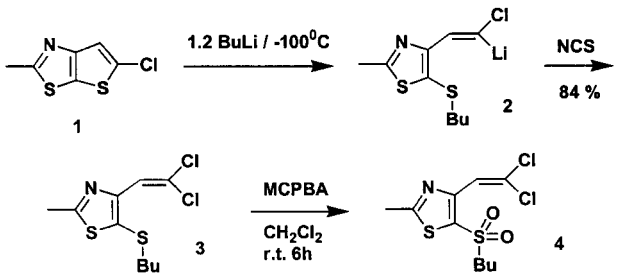
Abstract: Organolithium reagents can add to the sulfur atom of thiophenes that are substituted by a chlorine atom and fused to another aromatic system, at -78°C, to give ortho-substituted aryl sulfides.

While working on thieno[3,2-d]thiazole **1**[1], we encountered an unexpected reaction. Treatment of **1** with butyllithium at -100°C and addition of N-chlorosuccinimide yielded a product containing a butyl group and an extra chlorine atom. This unknown compound was then oxidized to the sulfone **4**, which was identified by X-ray crystallography (scheme 1 and figure 1). This addition product could be explained by the addition reaction of the butyl group to the sulfur atom of the thiophene, with subsequent ring opening and trapping of the vinylic anion **2** with N-chlorosuccinimide.



Scheme 1

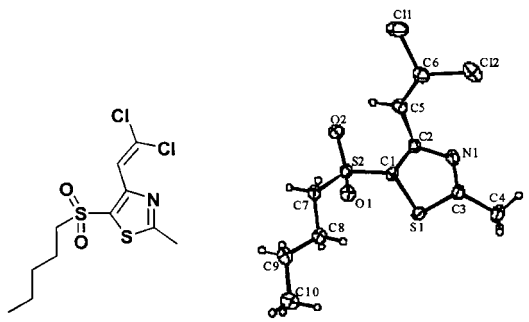
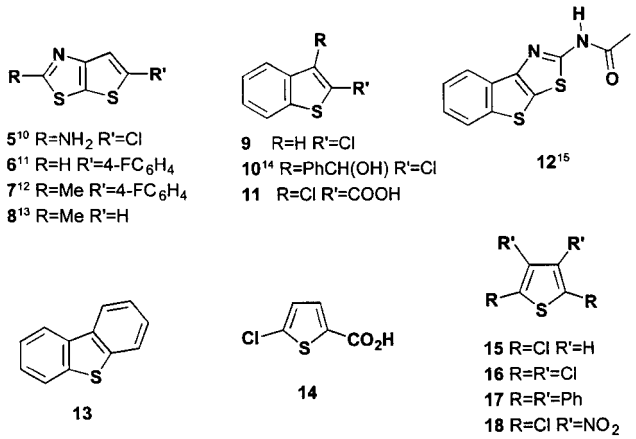


Figure 1. X-ray structure of sulfone **4**

Although addition of alkyllithiums to sulfur in thioethers[2], disulfides[3] and dithioketals[4] is known, there are few reports on addition to a sulfur atom included in an aromatic heterocycle with subsequent ring cleavage; known heterocycles reacting this way are imidazo[2,1-b]benzothiazoles[5], 1,4-dithiins[6] and isothiazoles[7]. Evidences for the addition of butyl- and phenyllithium to thiophenes were reported for 3,4-dichloro-2,5-dimethoxythiophene at room temperature, but the only products of the reaction were dibutyl and diphenyl sulfides respectively[8]. We wish to report in this paper examples of this addition reaction of organolithiums to thiophenes, at -78°C or below, and evidence supporting the proposed mechanism.

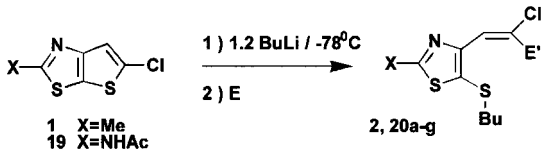
We first tried to determine what are the structural features that can promote such ring cleavage on a thiophene. Scheme 2 lists all the heterocycles that failed to give any addition of BuLi to the sulfur. In most cases, side reactions such as proton abstraction (thiophenes **5**-**9**, **12**, **14** and **15**) and lithium-chlorine exchange (**10**, **16**) compete effectively with the ring opening. In the absence of a chlorine substituent or an "acidic" proton, as in compounds **13** and **17**, there is no reaction at all, even in ether at room temperature. 2,5-Dichloro-3,4-dinitrothiophene **18** gave only decomposition products and the acid **11** is attacked to give the butyl ketone at -78°C.



Scheme 2

The only thiophenes we have found that react with BuLi by addition to the sulfur are represented by the two 2-chlorothieno[3,2-d]thiazoles **1** and **19**[9] (scheme 1 and table 1) and the fused thiophenes substituted by a chlorine atom in position 3 (table 2). In the case of the two 2-chlorothieno[3,2-d]thiazoles **1** and **19**, the intermediate anion **2** obtained after addition of an organolithium salt can be trapped with the more reactive electrophiles to yield substituted (E)-chloroalkenes **20** with retention of configuration. As shown in table 1, this anion is not nucleophilic enough to react with ethyl iodide and benzyl bromide.

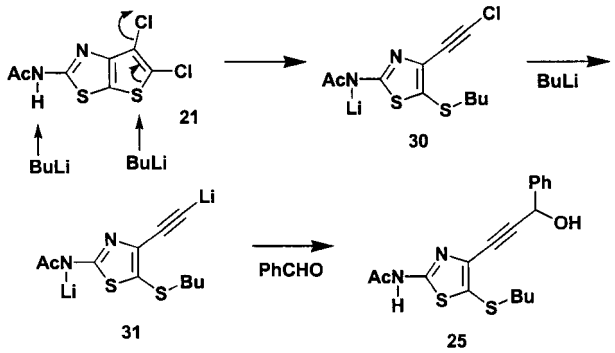
Table 1. Addition of electrophiles to the anion generated by BuLi attack on 5-chloro-2-methylthieno[3,2-d]thiazole



X	E	E'	#	Yield
Me	PhCHO	PhCH(OH)	**20a**	77
Me	NCS	Cl	**2**	84
Me	NH_4Cl	H	**20b**	75
Me	PhCOCl	PhCO	**20c**	62
AcNH	PhCHO	PhCH(OH)	**20d**	81[a]
AcNH	MeI	Me	**20e**	70[a]
AcNH	NCS	Cl	**20f**	56[a]
AcNH	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	**20g**	10[a]
AcNH	EtI	Et		0[a,b]
AcNH	$PhCH_2Br$	$PhCH_2$		0[a,b]

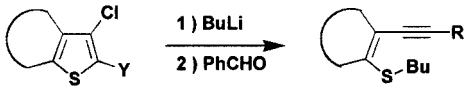
a) 2.2 equiv. BuLi, b) **20b** was the major product

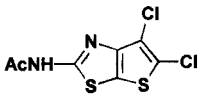
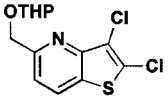
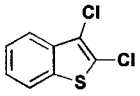
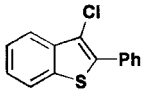
For the thiophenes of table 2, a slightly different pathway is followed by the reaction. The electron withdrawing effect of the 3-chloro substituent, along with its easy elimination, probably facilitates the addition of butyllithium to the sulfur to give the chloroalkyne **30** (scheme 3). Then lithium-chlorine exchange gives the alkyne anion **31** which adds to the electrophile. Addition of BuLi to the thieno[3,2-d]thiazole **21** and lithium-chlorine exchange with the chloroalkyne intermediate **30** compete with each other. In the presence of 2.2 equivalents of BuLi, the ratio of products **25**:**26** is 1:2, while use of 3.3 equivalents gave a ratio of 2:1. In the last three entries of table 1, the chloroalkyne was not detected when an excess of BuLi was added. It should also be noted that the benzylic alcohols **25**, **27** and **28** are slowly oxidized by air to give the corresponding phenyl ketones.



Scheme 3

Table 2. Reaction of 3-chlorothiophenes with BuLi

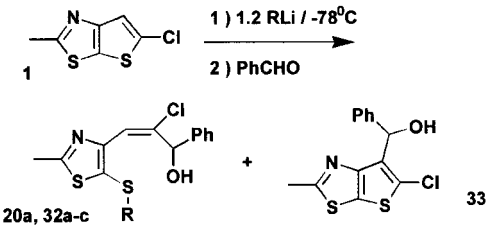


#	Thiophene	T (°C)	#	Product R	Yield (%)
21[16]		-78[a]	25	PhCH(OH)	63
			26	Cl	32
22[17]		-100[b]	27	PhCH(OH)	82
23[18]		-78[b]	28	PhCH(OH)	71
24[19]		-78[c]	29	Ph	71

a) 3.3 equiv. BuLi, b) 2.3 equiv. BuLi, c) 1.2 equiv. BuLi; hydrolysis with sat. NH_4Cl at -78°C

We then tried to determine which organometallic species can give rise to this attack on the sulfur atom of thiophenes and found that this is specific to aryl- and alkyllithium salts; Grignard, cuprate, organozinc reagents, as well as cyanide, lithium enolates, lithium triethylborohydride (Super-Hydride) and diisobutylaluminum hydride did not react at all. The reaction with organolithiums is not general: the more basic sec-BuLi affords preferentially products arising from hydrogen abstraction while the behavior of tert-BuLi and PhLi toward the thiophene ring vary with the structure of the substrate (tables 3 and 4).

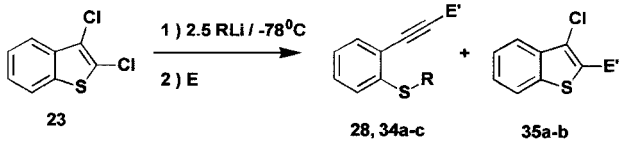
Table 3. Organolithium reaction with 5-chloro-2-methylthieno-[3,2-d]thiazole



R	#	Yield[a]	#	Yield[a]
Me	**32a**	35	**33**	5
n-Bu	**20a**	77		
sec-Bu	**32b**	22	**33**	31
tert-Bu	**32c**	54		
Ph		no reaction		

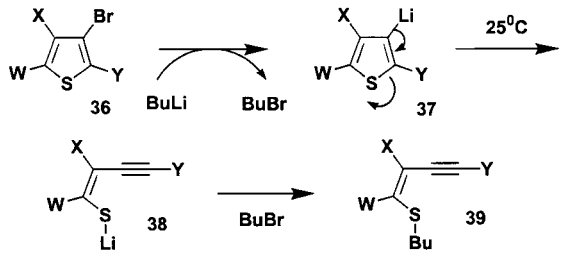
a) unoptimized yields

Table 4. Organolithium reaction with 2,3-dichlorobenzo-[b]thiophene



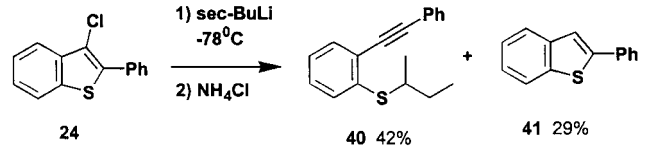
R	E	#	Yield	#	Yield
Me	PhCHO	**34a**	79		
n-Bu	PhCHO	**28**	71		
sec-Bu	NH_4Cl	**34b**	12	**35a**	80
tert-Bu	PhCHO			**35b**	93
Ph	NH_4Cl	**34c**	36	**35a**	51

Ring opening of thiophenes[20] and other sulfur containing heterocycles[7a,21] was reported to occur via another route (scheme 4). 3-Bromothiophene **36** can be metallated in position 3 and cleavage of the thiophene ring can then occur at room temperature in ether. The thiolate anion **38** can add to an electrophile such as butyl bromide (generated in the first step or added later during the reaction). Product **29** (table 2) was obtained by this method from 3-bromo-2-phenylbenzo[b]thiophene[20b] (the bromo analog of **24**). We do not believe that this mechanism is operating here for the following reasons: 1) the ring opening reported in this paper occurs at -78°C or below while ring opening of 3-lithiothiophenes happens at room temperature, 2) the products **3** and **20a-g** (scheme 1 and table 1), along with the addition products obtained with t-BuLi (**32c**, table 3) and PhLi (**34c**, table 4), cannot be rationalized using this mechanism, 3) addition of sec-BuLi to **24** and hydrolysis with NH_4Cl produced the sec-butyl thioether **40** (scheme 5) which cannot arise from the attack of the thiolate **38** on



Scheme 4

sec-butyl chloride at -78°C[22] and 4) lithium chlorine exchange on a 2,3-dichlorothiophene would occur preferentially with the 2-chloro substituent.



Scheme 5

In summary, fused thiophenes substituted by at least one chlorine can react with organolithium reagents, at -78°C, by addition to the sulfur. The anion generated after ring opening can then add to electrophiles or give elimination products when there is a leaving group in position 3 of the thiophene ring. The reaction is not general and is highly dependent on the substitution pattern of the thiophene and the nature of the organolithium species. Side reactions, such as proton abstraction and lithium-chlorine exchange, compete with the ring opening. Thiophenes that are not fused to another aromatic ring do not give rise to this reaction, the only known exception being 3,4-dichloro-2,5-dimethoxythiophene at room temperature[8].

Typical experimental procedure[23]

4-(Butylthio)-5-(2,2-dichloroethenyl)- 2-methylthiazole **3**:
Butyllithium 1.6 M in hexane (2.4 ml, 3.36 mmol) was added dropwise to a solution of 5-chloro-2-methylthieno[3,2-d]thiazole **1** (544 mg, 2.87 mmol) in THF (8 ml) at -100°C under nitrogen. The mixture was stirred at -100°C for 5 min and a solution of N-chlorosuccinimide (795 mg, 5.95 mmol) in THF (8 ml) was then added slowly. The mixture was stirred at -78°C for 15 min and was quenched with saturated NH_4Cl. The product was extracted in ethyl acetate, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography with 2.5% EtOAc/hexane to yield 673 mg (84 %) of **3** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 2.74 (t, J=7.3 Hz, 2H), 2.69 (s, 3H), 1.55 (m, 2H), 1.40 (m, 2H), 0.90 (t, J=7.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.2 (C), 150.5 (C), 129.8 (C), 124.3 (C), 120.2 (CH), 38.5 (CH_2), 31.2 (CH_2), 21.5, 19.9, 13.5 (CH_3); IR (KBr) 3030, 2980, 2920, 2860, 1735, 1605, 1490, 1460, 1430, 1270, 1170, 1050, 900, 720 cm^{-1}; MS (+CI, CH_4) *m/z* 282 (M+1, 100), 284 (M+3, 78). Anal. Calcd for $C_{10}H_{13}Cl_2NS_2$: C, 42.56; H, 4.64; N, 4.96; S, 22.72; Cl, 25.12. Found: C, 42.85; H, 4.79; N, 4.94; S, 22.60; Cl, 24.92.

Acknowledgment

The authors are grateful to Dr R. G. Ball for the determination of the crystal structure of 4-(butylsulfonyl)-5-(2,2-dichloroethenyl)-2-methylthiazole **4**.

References and notes

1. Prepared by chlorination of 2-methylthieno[3,2-d]thiazole **8**[13] with trichloroisocyanuric acid (0.4 equiv., CH_2Cl_2, 0°C then r.t. 2h; 73% yield).
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9. Obtained by chlorination of 2-acetamidothieno[3,2-d]thiazole[13,24] with trichloroisocyanuric acid (0.5 equiv., CH_2Cl_2, 0°C then r.t. 2h; 51% yield).
10. Prepared from **19** (HCl, dioxane, reflux[13]).
11. Prepared from 5-bromothieno[3,2-d]thiazole[25] (4-$FC_6H_4B(OH)_2$, $Pd(Ph_3P)_4$, aq. Na_2CO_3, toluene / ethanol, 100°C 3h [26]).
12. Prepared as **6** from 2-methylthieno[3,2-d]thiazole **8**[13,25].
13. Paulmier, C. *Bull. Soc. Chim. Fr.* **1980**, II-151.
14. Prepared from **9** (BuLi, -100°C 5 min., PhCHO; 77% yield).
15. Prepared from 3-acetylbenzo[b]thiophene (1, $NH_2OH{\cdot}HCl$, $BaCO_3$; 2, PCl_5, ether; 3, Br_2, NH_4SCN; 4, 170°C, Dowtherm A[13,27]).
16. Obtained as a side product in the synthesis of **19**[9] (13% yield).
17. Young, R. N.; Labelle, M.; Leblanc, Y.; Xiang, Y. B.; Lau, C. K.; Dufresne, C.; Gareau, Y. *U.S.P. 5,472,964*, Dec. 5, 1995 (*Chem. Abstr*. **1996**, *124*, 232429d).
18. Prepared from benzo[b]thiophene (trichloroisocyanuric acid (1.0 equiv., CH_2Cl_2, 0°C then r.t. 2h; 36% yield).
19. Prepared from benzo[b]thiophene (1, BuLi, DME, -78°C; 2, $B(OiPr)_3$, -78°C to r. t.; 3, PhI, $(Ph_3P)_4Pd$, 2 M Na_2CO_3, reflux, 68% yield; 4, trichloroisocyanuric acid (0.4 equiv.), CH_2Cl_2, 0°C then r. t. 2h, 88% yield).
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22. Ring opening of 3-lithiobenzothiophene occurs only at room temperature[20b] and lithium thiophenolate doesn't react with sec-butyl chloride, even after 10 min. at room temperature in THF.
23. All new compounds gave satisfactory analytical and spectroscopic data. Selected data: 4-(butylsulfonyl)-5-(2,2-dichloroethenyl)-2-methylthiazole **4**; m.p. 74.5-75.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 3.15 (m, 2H), 2.75 (s, 3H), 1.72 (m, 2H), 1.42 (m, 2H), 0.91 (t, J=7.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.4 (C), 150.7 (C), 132.1 (C), 129.1 (C), 118.7 (CH), 57.9, 24.7, 21.4, 19.9, 13.4 (CH_3); IR (KBr) 3080, 2970, 2950, 2880, 1610, 1490, 1470, 1440, 1340, 1300, 1290, 1240, 1180, 1140, 1080, 910, 860, 790, 770, 730, 670 cm^{-1}; MS (+CI, CH_4) *m/e* 316 (M+3), 314 (M+1), 279, 157; anal. calcd for $C_{10}H_{13}S_2O_2Cl_2N$: C, 38.22; H, 4.17; N, 4.46; S, 20.40; Cl, 22.56; found: C, 38.55; H, 4.18; N,

4.46; S, 20.20; Cl, 22.35; (E)-2-(acetylamino)-4-butylthio-5-(3-hydroxy-3-phenyl-2-chloropropen-1-yl)thiazole **20d**; m.p. 141-142°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 7.40-7.37 (m, 2H), 7.20-7.16 (m, 3H), 7.10 (s, 1H), 6.06 (s, 1H), 2.72 (t, J=7.3 Hz, 2H), 2.22 (s, 3H), 1.55-1.50 (m, 2H), 1.42-1.36 (m, 2H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.6, 158.2, 145.9, 140.2, 139.2, 128.2, 127.7, 126.2, 123.7, 120.2, 75.9, 38.3, 31.3, 22.9, 21.5, 13.5; IR (KBr) 3500, 3240, 3190, 3060, 2960, 2930, 1680, 1535, 1370, 1325, 1310, 1280, 1260, 1060, 1040, 700 cm^{-1}; MS (FAB+, NBA) *m/z* 396 (M+, 44), 397 (M+1, 34), 398 (M+2, 24), 399 (M+3, 13), 379 (100), 303 (98); anal. calcd for $C_{21}H_{18}N_2S_2O_2Cl$: C, 54.46; H, 5.33; N, 7.06; S, 16.15; Cl, 8.93; found: C, 54.53; H, 5.47; N, 7.12; S, 16.25; Cl, 8.74; 3-(butylthio)-2-(3-hydroxy-3-phenylprop-1-yn-1-yl)-6-((2H)-tetrahydropyran-2-yloxymethyl)pyridine **27**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2H), 7.56 (d, 1H), 7.38 (m, 4H), 5.75 (s, 1H), 4.82 (d, 1H), 4.71 (t, 1H), 4.58 (d, 1H), 3.87 (m, 1H), 3.51 (m, 1H), 2.89 (t, 2H), 1.62 (m, 8H), 1.44 (m, 2H), 0.91 (t, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.5, 140.2, 140.0, 136.4, 135.3, 128.5 (2C), 128.3, 127.0 (2C), 121.2, 98.6, 95.1, 83.7, 69.2, 64.9, 62.3, 32.1, 30.7, 30.5, 25.3, 21.9, 19.4, 13.6; IR (KBr) 3200, 2950, 2220 cm-^{1}; MS (+CI, CH_4) *m/e* 452 (M-C_3H_5), 440 (M-C_2H_5), 412 (M+1), 394 (M-OH); 3-(2-(methylthio)phenyl)-1-phenylprop-2-yn-1-ol **34a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H), 7.40 (m, 3H), 7.30 (m, 2H), 7.14 (d, 1H), 7.08 (t, 1H), 5.76 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 141.6, 140.3, 132.4, 128.9, 128.4 (2C), 128.2, 126.7 (2C), 124.1, 124.0, 120.4, 94.9, 84.0, 65.1, 14.9; IR (NaCl) 3390, 3060, 2920, 2220 cm-^{1}; MS (+CI, CH_4) *m/e* 295 (M+C_3H_5), 283 (M+C_2H_5), 237 (M-OH).

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