Base-Catalyzed Halogen Dance Reaction at Thiophenes: A Spectroscopic Reinvestigation of the Synthesis of 2,5-Dibromo-3-(trimethylsilyl)thiophene

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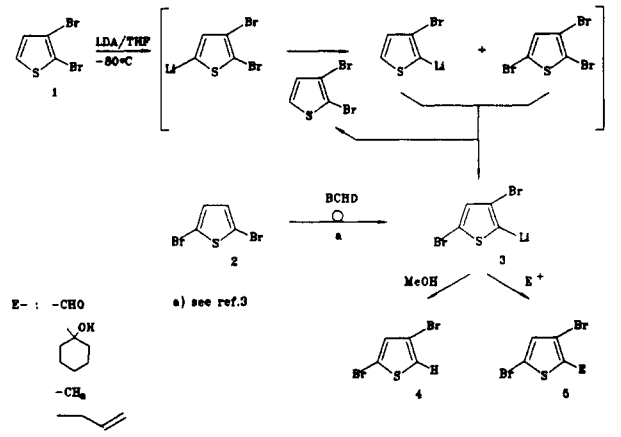
Summary: Reacting 2,5-dibromothiophene with LDA and quenching with trimethylsilyl chloride yielded 3,5-dibromo-2-(trimethylsilyl)thiophene (8) and not the title compound 2,5-dibromo-3-(trimethylsilyl)thiophene (**7a**)—an interesting starting material for polythiophene synthesis—as claimed in the literature.[3,7,8]

It is well known in the literature that α-halothiophenes in strong basic media suffer rearrangement reactions resulting in the formation of thermodynamically more stable products.[1-4] This fact was explained by proposing a base-catalyzed halogen dance (BCHD) mechanism: via an initial metalation of the starting compound subsequent rapid metal–halogen exchange between the metalated species thus obtained and unreacted starting material or polyhalogenated intermediates, respectively, a final product is formed, showing a halogen migration.[5] Recently we have investigated and published a new example of this reaction type: after reacting 2,3-dibromothiophene (**1**) with 1 equiv of LDA at −80 °C in dry THF and quenching with various electrophiles a series of 2-substituted 3,5-dibromothiophenes **5** were obtained in very good yields (Scheme I).[6] No formation of 5-substituted 2,3-dibromo-isomers was observed under the reaction conditions described.

The products obtained were identical with those from an analogous reaction starting from a different educt: Kano and co-workers[3] reacted the easier available 2,5-dibromothiophene (**2**) with LDA at −80 °C, yielding the same rearranged lithium intermediate **3** as detected within our BCHD reaction: this could be proved by us unambigously by quenching both experiments with dry MeOH at −80 °C, yielding only 2,4-dibromothiophene (**4**).

Reviewing the literature for similar reaction types at thiophene we found one remarkable example for selective β-metalation of 2,5-dibromothiophene without rearrangement of the initially formed 3-lithio-2-halo intermediate **6**. According to Davies[7] compound **2** was reported to give upon reaction with LDA and quenching with trimethylsilyl chloride (TMSCl) not—as expected and true with a series of other electrophiles—a 2-substituted 3,5-dibromothiophene but a 2,5-dibromo-3-(trimethylsilyl)thiophene (**7a**) (there were no experimental or spectroscopic data given for this reaction). This surprising result was uncritically cited by Kano[3] and confirmed synthetically and NMR spectroscopically by Zimmer,[8] who extended the scope of the reaction for preparing also 3-substituted selenyl and stannyl derivatives **7b–d** of 2,5-dibromothiophene (Scheme II).[9]

Scheme I



Scheme II

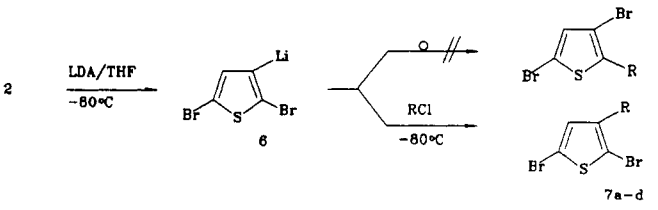


Table I. Comparison of the ^{13}C NMR and ^{1}H NMR Spectral Data for Postulated Structure 7a[a] and Compound 8[b]

	^{13}C NMR		
compd	δ (ppm)	carbon assignment	(increment values),[c] δ (ppm)
7a[a]	116.5	C_2	(117.8)
	137.4	C_3	(144.5)
	134.4	C_4	(134.7)
	116.5	C_5	(112.1)
	-0.8	C_6	–
8	116.4	C_3	(116.6)
	137.5	C_2	(139.2)
	134.4	C_4	(133.1)
	116.4	C_5	(118.2)
	-0.9	C_6	–

	^{1}H NMR	
compd	hydrogen	δ (ppm)
7a	H_4	7.00
	CH_3	0.33
8	H_4	7.02
	CH_3	0.37

[a] Data from ref 8. [b] Reference 10. [c] Reference 11.

(1) (a) Moses, P.; Gronowitz, S. *Ark. Kem.* **1961**, *18*, 119. (b) Gronowitz, S. *Adv. Heterocycl. Chem.* **1963**, *1*, 75.

(2) (a) Reinecke, M. G.; Adickes, H. W.; Pyun, C. *J. Org. Chem.* **1971**, *36*(18), 2690. (b) Reinecke, M. G.; Hollingworth, T. A. *J. Org. Chem.* **1972**, *37*(26), 4257.

(3) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1983**, *20*(10), 2035.

(4) Grosvenor, P. R.; Fuller, L. S. Eur. Pat. Appl. 88201494.7, 12.07.88.

(5) (a) Reinecke, M. G.; Adickes, H. W. *J. Am. Chem. Soc.* **1968**, *90*, 511. (b) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139. (c) Taylor, E. C.; Vogel, D. E. *J. Org. Chem.* **1985**, *50*(7), 1002.

(6) Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* **1989**, 771.

(7) Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 3507.

(8) Pham, C. v.; Macomber, R. S.; Mark, H. B., Jr.; Zimmer, H. *J. Org. Chem.* **1984**, *49*(26), 5250.

0022-3263/90/1955-2993$02.50/0

Table II. Carbon Shifts and C–H Coupling Constants for 2- and 3-(Trimethylsilyl)thiophene (9 and 10)[a]

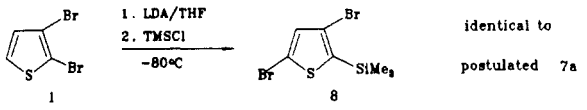
	δ (ppm)				J, Hz			
compd	C_2	C_3	C_4	C_5	J_{C2-H2}	J_{C3-H3}	J_{C4-H4}	J_{C5-H5}
9	139.9	133.9	128.0	130.2	–	164.8	167.2	185.5
10	131.2	141.0	131.2	125.5	183.7	–	164.8	184.3

Chemical Shifts of 2- and 3-(Trimethylsilyl)thiophene Relative to the α- and β-Carbons of Thiophene in $CDCl_3$[b]

	δ (ppm)			
compd	C_2	C_3	C_4	C_5
9	15.0	7.2	1.3	5.3
10	6.3	14.3	4.5	0.6

[a] Reference 10. [b] Reference 12.

Scheme III



The possibility for selective formation of these 3-metalated and subsequently substituted products was contradictive to our experience with BCHD reactions.

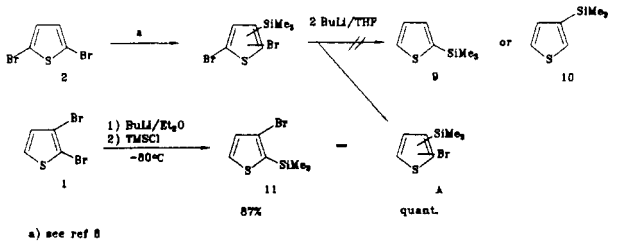
Therefore we reacted trimethylsilyl chloride according to our published BCHD procedure[6] with 2,3-dibromothiophene and LDA in THF and obtained—via the intermediacy of thienyllithium **3**—3,5-dibromo-2-(trimethylsilyl)thiophene (**8**) (Scheme III).

Comparing the ^1H NMR and ^{13}C NMR data of 8 with the shift values published by Zimmer[8] for the compound supposed to be 2,5-dibromo-3-(trimethylsilyl)thiophene (**7a**) showed clearly that both compounds are *identical* (Table I). In consequence NMR spectroscopic and synthetic efforts have been undertaken to proof the constitution of postulated **7a** independently.

Therefore the ^{13}C NMR shift values of 2-(trimethylsilyl)thiophene (**9**) and 3-(trimethylsilyl)thiophene (**10**), both prepared according to published methods[13] (Table II), were correlated with those of 2,4-dibromothiophene (**4**) and 2,5-dibromothiophene (**2**).[11] Comparing the values incremented for the structure proposed by Zimmer with the experimental ones exhibited a significant difference, while the data of 8 were in agreement with the calculated values (Table I).

To have absolute certainty we repeated a silylation reaction strictly analogous to Zimmer's conditions (slow addition of starting material **2** to 1.1 equiv of LDA in THF at −78 °C; 30 min at −80 °C followed by slow addition of TMSCl at −80 °C and warming up to 0 °C).[8] The product obtained after workup was reacted with 2 equiv of BuLi in THF at −80 °C. It was planned to synthesize upon hydrolysis a dehalogenated trimethylsilyl-substituted thiophene and to compare its NMR shifts with the reference data of the silylthiophenes **9** and **10** for elucidating the structure of **7a**. But in spite of varying the reaction parameters, such as employing an excess of 1 equiv of BuLi and elevated temperatures (0 °C), only one bromine atom could be removed. A 2,3-disubstituted thiophene (J_{H4-H5} = 4.9 Hz) (A) was isolated as the only product (Scheme IV).

Scheme IV



Scheme V

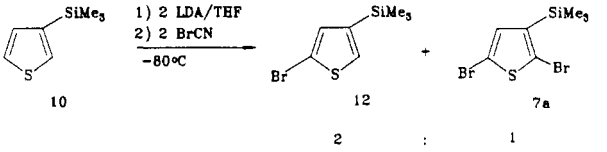


Table III. Comparison of the ^{13}C NMR Spectral Data for Product A and the Increment Shift Values for the Two Possible Isomers[a,b]

compd	carbon	δ (ppm)	(increment values)[b] δ (ppm)
A	C_2	134.1	
	C_3	117.2	
	C_4	130.5	
	C_5	132.4	
2-bromo-3-TMS-thiophene	C_2		(118.2)
	C_3		(143.9)
	C_4		(131.9)
	C_5		(127.3)
3-bromo-2-TMS-thiophene (11)	C_2		(137.4)
	C_3		(117.0)
	C_4		(130.9)
	C_5		(131.6)

[a] Reference 10. [b] Reference 11.

Comparing the incremented NMR shifts for both possible structures, 2-bromo-3-(trimethylsilyl)thiophene or 3-bromo-2-(trimethylsilyl)thiophene, respectively, with the experimentally obtained values for the isolated mono halogenated thiophene A, gave strong indication for the latter one (Table III).

(9) In continuation of this work some papers on polythiophenes trusting on these postulated structures **7a–d** as monomeric starting compounds have been published: (a) Czerwinsky, A.; Zimmer, H.; Amer, A.; Pham, C. v.; Pons, S.; Mark, H. B., Jr. *J. Chem. Soc., Chem. Commun.* **1985**, 1158. (b) Pham, C. v.; Czerwinsky, A.; Zimmer, H.; Mark, H. B., Jr. *J. Polym. Sci., Polym. Lett.* **1986**, *24*, 103. (c) Czerwinsky, A.; Cunningham, D. D.; Amer, A.; Schrader, J. R.; Pham, C. v.; Zimmer, H.; Mark, H. B., Jr. *J. Electrochem. Soc.* **1987**, *134*(5), 1158.

(10) All NMR spectra were recorded in $CDCl_3$.

(11) The incremented chemical shifts for silylated bromothiophenes were calculated by adding the increments we have evaluated for the trimethylsilyl substituent (see Table II) to the shifts of appropriate bromothiophenes in $CDCl_3$. 2,3-Dibromothiophene (**1**): 111.1 (C_2), 113.9 (C_3), 126.8 (C_5), 129.9 (C_4). 2,5-Dibromothiophene (**2**): 111.5 (C_2, C_5), 130.2 (C_3, C_4) (see also ref 8). 2,4-Dibromothiophene (**4**): 109.4 (C_4), 112.9 (C_2), 124.2 (C_5), 131.8 (C_3). 2-Bromothiophene: 111.9 (C_2), 126.7 (C_5), 127.4 (C_4), 129.6 (C_3). 3-Bromothiophene: 109.8 (C_3), 122.4 (C_2), 126.3 (C_5), 129.6 (C_4). The carbon assignments are according to Reinecke, M. G., Pedaja, P. In *The chemistry of heterocyclic compounds*; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons, Inc.: New York, 1986, Vol. 44/2, Chapter III, pp 463–466. The shift data reported herein are, as they have been recorded neat or in acetone-d_6, slightly different from our values obtained in $CDCl_3$.

(12) Thiophene ^{13}C NMR ($CDCl_3$): δ 124.9 (C_2, C_5), 126.7 (C_3, C_4).

(13) Effenberger, F.; Häbich, D. *Justus Liebigs Ann. Chem.* **1979**, 842.

Table IV. ^{13}C NMR and ^{1}H NMR Spectral Data for 2,5-Dibromo-3-(trimethylsilyl)thiophene 7a Obtained by Independent Synthesis[a]

		^{13}C NMR		
compd	carbon	δ (ppm)	(increment values)[b] δ (ppm)	(ref 8) δ (ppm)
7a	C_2	117.8	(117.8)	(116.5)
	C_3	142.5	(144.5)	(137.4)
	C_4	135.2	(134.7)	(134.4)
	C_5	111.1	(112.1)	(116.5)
	C_6	-0.9	-	(-0.8)
compd	hydrogen	^{1}H NMR: δ (ppm)		(ref 8)
7a	H_4	6.83		(7.00)
	CH_3	0.34		(0.33)

[a] Reference 10. [b] Reference 11.

An unequivocal result was obtained by independent synthesis of 3-bromo-2-(trimethylsilyl)thiophene (11) (Scheme IV),[14] which was identical in physical and spectroscopical properties with compound A.

As a final synthetic proof for the wrong substitution pattern **7a–d** given in the literature we have prepared the postulated 2,5-dibromo-3-(trimethylsilyl)thiophene (**7a**) within a preliminary experiment (Scheme V) via a new pathway: by reacting 3-(trimethylsilyl)thiophene (**10**) with 2 equiv of LDA and 2 equiv of BrCN at -80 °C a 2:1 mixture of 2-bromo-4-(trimethylsilyl)thiophene (**12**) and the target compound **7a**, which could be isolated and purified by Kugelrohr distillation, was obtained.[15]

The spectroscopic shift values for **7a** are completely different from those published by Zimmer (Tables IV and I) who obviously also has obtained the rearranged 3,5-dibromo-2-(trimethylsilyl)thiophene (**8**). Therefore it can be stated without any doubt that interaction of one equivalent of LDA in THF/-78 °C with 2,5-dibromothiophene leads—via BCHD mechanism and upon quenching with any electrophile—only to products with a 3,5-dibromo pattern.

We are currently optimizing the synthesis of the new compound **7a** and investigating the dependence of the BCHD mechanism on various reaction parameters.

Acknowledgment. We are dedicating this paper to our Head, Prof. Dr. Fritz Sauter, on the occasion of his 60th birthday.

(14) 2,3-Bromothiophene (1) was reacted with 1 equiv of BuLi in dry Et_2O at -80 °C (similar to: Seconi, G.; Eaborn, C.; Stamper, J. G. *J. Organomet. Chem.* **1981**, *204*, 153) to form via metal–halogen exchange (3-bromo-2-thienyl)lithium. Subsequent quenching with TMSCl afforded product 11 in high yield (87% upon distillation) and without any side products. ^{1}H NMR ($CDCl_3$): δ 7.44 (d, 1 H, J_{AB} = 4.9 Hz), 7.09 (d, J_{AB} = 4.9 Hz), 0.40 (s, 9 H).

(15) To a stirred solution of 12.9 mmol of diisopropylamide in dry tetrahydrofuran (THF) at -80 °C was added 1 g (6.4 mmol) of **10** in 10 mL of dry THF rapidly. After being stirred for 30 min at -80 °C, a solution of 1.35 g (12.8 mmol) of cyano bromide in 10 mL of dry THF was added dropwise. Stirring was continued for 15 min, and then the solution was hydrolyzed. The organic phase was separated and dried (anhydrous Na_2SO_4), and the THF was evaporated. The resulting brown residue was distilled in vacuum. Fraction I: bp 150 °C (80 mm); yield 0.8 g (53%); no further purification; ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 1 H, J_{AB} = 1.2 Hz), 7.08 (d, 1 H, J_{AB} = 1.2 Hz), 0.26 (s, 9 H); ^{13}C NMR ($CDCl_3$) -0.9 (q), 112.5 (s, C_2), 132.7 (d, C_5), 133.8 (d, C_3), 142.9 (s, C_4). Fraction II: distilled twice; bp 150 °C (20 mm); yield 0.5 g (25%) of **7a**; spectroscopic data see Table IV. Anal. Calcd for $C_7H_{10}Br_2SSi$: C, 26.77; H, 3.21. Found: C, 27.02; H, 3.21.

[2,3] Wittig Rearrangement of Nonracemic Propargyloxyacetic Acids and Esters. Synthesis of Optically Active 2,5-Dihydrofurans

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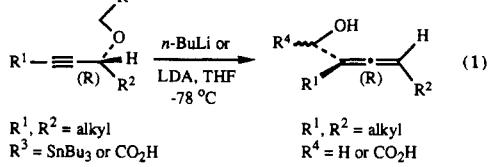
Summary: Optically active propargyloxyacetic acids **4**, available in ca. 90% ee through reduction of alkynones **2** with Chirald–$LiAlH_4$ followed by alkylation with chloroacetic acid, undergo highly stereoselective [2,3] rearrangement upon treatment with LDA in THF at -78 °C to afford α-(*S*)-hydroxy-β-(*R*)-allenic acids with complete transfer of chirality and >90% diastereoselectivity. The diastereomeric methyl ester derivatives **5a** and **13** cyclize stereospecifically to trans and cis 1,5-dihydrofurans upon treatment with $AgNO_3$–$CaCO_3$, PhSeCl, or NBS.

We recently disclosed a new application of the [2,3] Wittig rearrangement in which nonracemic propargyl (tributylstannyl)methyl ethers and α-(propargyloxy)acetic acids afford optically active allenylcarbinols and α-hydroxy-β-allenic carboxylic acids with complete chirality transfer (eq 1).[1] Additional studies have now shown that such rearrangements of the acetic acid and related acetic ester systems are highly diastereoselective as well. Furthermore, the derived α-hydroxy ester products are readily and stereospecifically converted to 2,5-dihydrofurans.



The (propargyloxy)acetic acids **4** utilized in this preliminary study were prepared along the lines of our previous report as outlined in Scheme I.[1] Reduction of the alkynones **2** with Chirald–$LiAlH_4$[2] afforded propargylic alcohols **3** of ca. 90% ee as judged by ^{1}H NMR analysis of the *O*-methyl mandelates.[3] Base treatment of acid **4a** with 2.5 equiv of LDA in THF at -78 °C followed by esterification led to the allenic ester **5a** as a 93:7 mixture of diastereomers in 80% yield. Acid **4b** was similarly converted to ester **5b** as a 91:9 mixture of diastereomers in 48% yield along with an equal amount of elimination product **6b** (1:1 *E*:*Z*). The configuration of **5a** was ascertained by ^{1}H NMR analysis of the *O*-methylmandelates

(1) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854.

(2) Aldrich Chemical Co. Chirald is a trade name for Darvon alcohol. Cf. Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.

(3) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovic, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

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