Pergamon

Tetrahedron Letters, Vol. 35, No. 45, pp. 8481-8484, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01789-1

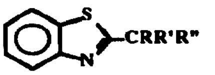
Self-Condensation of Benzothiazolylchloromethyllithiums.

Saverio Florio,*[a] Vito Capriati,[a] Maria Cristina Solimini[a] and Luigino Troisi[b]

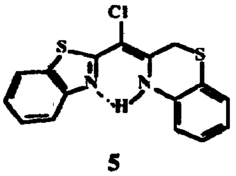
a)Dipartimento Farmaco-Chimico, Università di Bari, Traversa 200 Re David 4, 70125 Bari, Italy
b)Dipartimento di Biologia, Università di Lecce, Via Monteroni, 73100, Lecce, Italy

Abstract: Benzothiazolylchloromethyllithium **1c** and benzothiazolyldichloromethyllithium **1e**, easily available by lithiation of **1b** and **1d** (or **1f**) respectively, undergo a different type of self-condensation reaction giving **5** and **7a** respectively. The possibility that **1c** and **1e** behave as halocarbenoids is discussed.

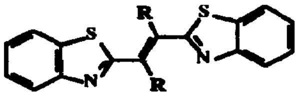
We have recently reported that benzothiazolylchloromethyllithium **1c**, promptly available by lithiation of chloromethylbenzothiazole **1b**, reacts with carbonyl compounds to furnish benzothiazolyl substituted oxiranes.[1] In view of the possible synthetic exploitation of α-haloorganolithiums of the kind of **1c**, we decided to study in more details the lithiation reaction of **1b** as well that of dichloro- and trichlorobenzothiazole **1d** and **1f**.



1a: R=OH; R'=R"=H
1b: R=Cl; R'=R"= H
1c: R=Cl; R'=Li; R"=H
1d: R=H; R'=R"=Cl
1e: R=Li; R'=R"=Cl
1f: R=R'=R"=Cl
1g: R=R'=Cl; R"=CCl$_2$BT
1h: R=Li; R'=Cl; R"=Bu^n
1i: R=R'=Bu^n; R"=H



5



7a: R = Cl; **7b**: R = Bu^n

When **1b**[2] was submitted to lithiation with lithium diisopropylamide at -78°C and the resulting dark brown solution of **1c** allowed to warm to room temperature, a solid yellow product formed in high yield. The ^{1}HNMR spectrum of such a compound showed a singlet (δ= 3.90 , 2H), eight aromatic protons and a singlet (δ= 12.4, 1H) which exchanged with D_2O. Moreover, ^{13}CNMR showed sexteen different carbons. These data, combined with elemental analysis and MS data[3] were consistent with structure **5**, as unequivocally confirmed by the X-Ray analysis (Fig. 1). A likely explanation for the formation of **5** is illustrated in Scheme 1. The α-chloromethyllithium **1c** would add to the C-N double bond of **1b** giving the thiazole-thiazoline intermediate **2**, which is stabilized by the intramolecular chelation of lithium. Such an addition is worth noting considering that thiazoles and benzoderivatives are rather reluctant to undergo nucleophilic addition to the C-N double bond. A preliminary activation of the aza group of the thiazole system via alkylation or acylation, that makes the 2-carbon more electrophilic, is usually required.

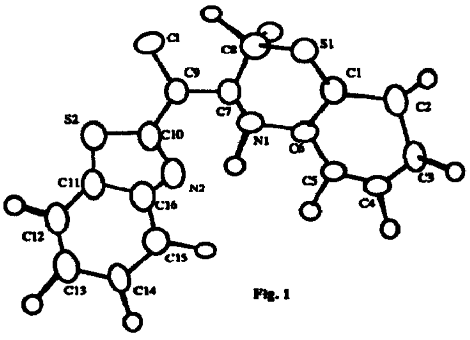
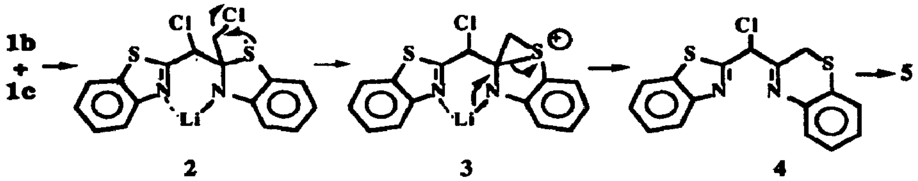


Fig. 1

Scheme 1

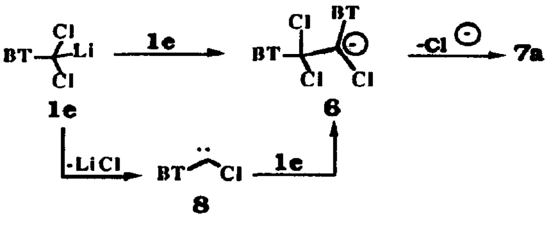


Only very strong nucleophiles such as carbanions add to the C-N double bond of unactivated thiazoles.[4] Strong electron-withdrawing substituents in the benzene ring also render the C-2 position sufficiently electrophilic to undergo nucleophilic addition.[5] The thiazoline system of intermediate **2** would then undergo ring enlargment *via* an anchimerically assisted nucleophilic substitution of chlorine to give, through the intermediate **3**, compound **4** that equilibrates to **5**, which is favored by the intramolecular hydrogen bond as confirmed by the strong deshielding of the H-N proton in the ^{1}HNMR.

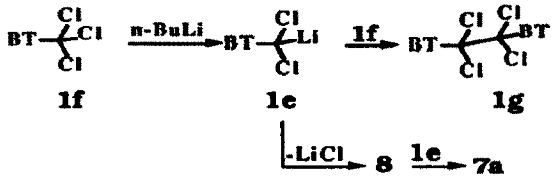
The conversion **1b** to **5** is a new example of unactivated thiazole-thiazine ring expansion. Indeed, examples of thiazole-thiazine ring expansion, a synthetically useful reaction,[6] are known, but in all of the reported cases, however, the reaction takes place only if a preliminary activation of the thiazole system by quaternization of the aza group is effected.[7-10]

Differently from **1b**, lithiation of dichloromethylbenzothiazole **1d**[11] with LDA at -78°C and warming to RT, gave dichlorodibenzothiazolylethene **7a** (60% yield). As shown in Scheme 2, the formation of compound **7a** might be envisaged as the result of a sort of "dimerisation" reaction between two moles of **1e** (one acting as a nucleophile and one as a carbenoid[12]) to give **6**, which undergoes elimination to produce **7a**. The formation of **7a** might also involve the intermediacy of carbene **8**, which would form from **1e**. Nucleophilic attack of **1e** to **8** would give **6**.

Scheme 2.

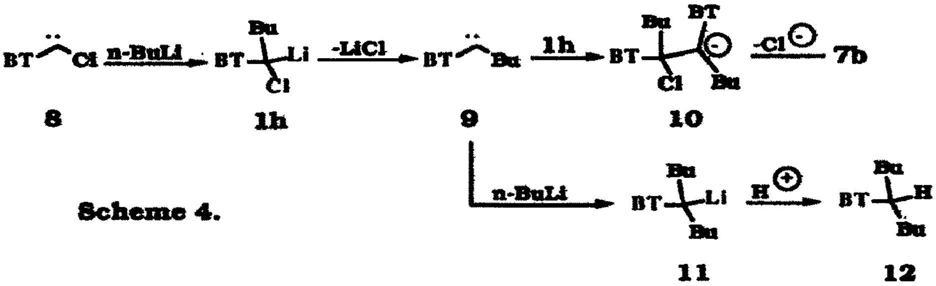


Support to this hypothesis comes from the fact that lithiation of trichloromethylbenzothiazole **1f**[11] with *n*-BuLi leads to the formation of **7a** too (25% yield).[13] This is likely the result of a dimerisation reaction between **1e**, derived from **1f** by chlorine-lithium exchange, and carbene **8**, which might originate from the same **1e** by elimination of LiCl. The homocoupling reaction between **1e** and **1f** would have given the tetrachloroethane **1g**, which, however, was not observed.



Scheme 3.

Moreover, the addition of an excess of n-BuLi (4 equiv.) to **1f** gave dibutyldibenzothiazolylethene **7b**.[13,14] A possible explanation for its formation is provided in Scheme 4. According to this scheme, carbene **8**, generated from **1e** by LiCl elimination, reacts with n-Buli to give **1h**; LiCl elimination would give carbene **9**. Its reaction with **1h**, followed by elimination, would furnish **7b**. In a different experiment, in which **1f** was added to n-BuLi, the GC-MS inspection of the reaction mixture indicated the formation of nonylbenzothiazole **12**, which is likely the result of the reaction of **9** with n-BuLi.[15] Attempts to trap carbenes **8** and **9** with alkenes, however, failed.[16]



Scheme 4.

In conclusion, in the present communication we have shown that benzothiazolylchloromethyllithiums such as **1c** and **1e** behave as α-halocarbenoids showing nucleophilic as well as electrophilic properties. They represent a new kind of heterosubstituted α-haloorganolithiums, which appear to be useful for the functionalisation of the benzothiazole system in the side chain. Moreover, we report here a new example of thiazole-thiazine ring expansion, which does not require the aza-activation. The determining step of the whole process of ring enlargement might be the formation of the intermediate **2**, which is stabilized by the intramolecular chelation. The reaction seems to be sensitive to steric hindrance as it occurs with **1c** but not with **1e**.

Acknowledgements: We thank the Italian CNR and MURST, Rome, for financial support and Prof.Giovanna Gasparri Fava, Università di Parma, Italy, for the X-RAY analysis

References.

1. Florio S., and Troisi L., *Tetrahedron Lett.*, 1992, 33, 7953.
2. 2-Chloromethylbenzothiazole **1b** can be prepared from 2-hydroxymethylbenzothiazole **1a** as in Ref. 6 or as reported in: Zubarovskii V. M., *Zhur. Obschei Khim*, 1954, 24, 1664. *Chem. Abstr.*,

1955, 49, 13223. **1b** can also be prepared from **1a** and CH_3SO_2Cl according a procedure described for other alcohols. Altamura M., and Perrotta E., *J. Org. Chem.*, **1993**, 58, 272.

3. Compound **5** formed in 85% yield and had the following data: yelow needles, m.p. 113°C (dec.). ^{1}HNMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 2H), 6.89-7.88 (m, 8H), 12.39 (s, 1H, exchange with D_2O). ^{13}CNMR (200 MHz, $CDCl_3$) δ: 26.78, 96.34, 117.76, 120.14, 121.18, 121.32, 122.33, 124.02, 126.24, 127.07, 128.19, 133.15, 136.87, 139.46, 153.71, 168.60. MS, m/e: 331.25 (M+1, 198), 330.25 (M^+, 1000), 297.30 (M^+-SH, 748), 294.30 (M^+- HCl, 439), 262.25 (863). Elem.Anal.: calcd. for $C_{16}H_{11}ClN_2S_2$: C 58.09, H 3.35, N 8.47. Found: C 60.00, H 4.04, N 8.08.
4. The addition of strong nucleophiles to the C-N double bond of thiazoles and benzothiazoles has been reported: Meyers A. I., and Knaus G. N., J. Am. Chem. Soc., **1973**, 95, 3408; Florio S., Epifani E., Ingrosso G., and Sgarra R., *Tetrahedron*, **1984**, 40, 5089 and Refs. therein.
5. Aresta M., Ciminale F., *J. Chem. Soc. Dalton Trans.*, **1981**, 1520 and Refs. therein
6. Gupta R. R., in "*Phenothiazines and 1,4-Benzothiazines, Chemical and Biomedical Aspects*", Elsevier, New York, **1988**, Vol. 4, chapter 2, pag. 163-269.
7. Friedrich W., Krohnke F., and Schiller P., *Chem. Ber.*, **1965**, 98, 3804.
8. Federsel H. J., and Bergman J., *Tetrahedron Lett.*, **1980**, 21, 2429.
9. Van Allan J.A., Mee J. D., Maggiulli C. A., and Henion R. S., *J. Heterocyclic Chem.*, **1975**, 12, 1005.
10. McKillop A., Sayer T. S. B., and Bellinger G. C. A., *J. Org. Chem.*, **1976**, 41, 1328.
11. 2-Benzothiazolyldichloromethane **1d** and 2-benzothiazolyltrichloromethane **1f** were obtained as a by-product in the preparation of **1b** from **1a** and $SOCl_2$.**1d**: m.p.: 71°-73°C; ^{1}H-NMR (90 MHz, $CDCl_3$,) δ: 7.1 (s, 1H), 7.4-7.7 (m, 2H), 7.8-8.2 (m, 2H). MS, m/e: 217 (M^+, 192), 219 (M+2, 129), 221 (M+4, 24), 184 (383), 182 (999), 146 (421). **1f**: m.p. 37.5° - 38,5°C. ^{1}H-NMR (90 HMz, $CDCl_3$) δ; 7,4-7.7 (m, 2H) 7.8-8.2 (m, 2H); MS, m/e: 251 (M^+ ,138), 253 (M+2, 138), 255 (M+4, 47), 257 (M+6, 6), 220 (129), 218 (699), 216 (1000), 183 (19), 181 (48), 148 (8), 146 (156).
12. For reviews on halocarbenoids see: Kobrich G., *Angew. Chem. Int. Ed. Engl.*, **1972**, 11, 473; Siegel H., *Top. Curr. Chem.*, **1982**, 106, 55 and Refs. therein.
13. Compounds **7a** and **7b** showed the following data: **7a**: m.p. 128°C. ^{1}HNMR (300 MHz,$CDCl_3$) δ: 7.30-7.60 (m, 2H), 7.78-8.00 (m, 2H). ^{13}CNMR (200 MHz, $CDCl_3$) δ: 161.11, 152.57, 136.34, 129.46, 126.67, 126.48, 124.40, 121.55. MS, m/e: 362 (M^+, 1), 364 (M+2, 1), 329 (433), 328 (202), 327 (1000), 292 (90), 291 (55). Elem.Anal.: Calcd. for $C_{16}H_8Cl_2N_2S_2$: C 53.0, H 2.21, N 7.73. Found: C 53.1, H 2.21, N 7.70. **7b**: MS, m/e: 406 (M^+, 270), 363 (1000), 349 (633), 321 (60), 307 (104), 228 (125), 214 (104), 200 (92), 186 (125).
14. **7b** tends to decompose and could be isolated for characterisation only in about 10% yield.
15. A comparable behaviour has been recently reported for benzyl ethers: Boche G., Bosold F., Lohrenz J.C.W., Opel A., and Zulauf P., *Chem. Ber.* **1993**, 126, 1873.
16. Boche has recently reported in Ref.14 that cyclopropanation of alkenes with heterosubstituted carbenes occurs only in very low yield.

(*Received in UK* 1 *August* 1994; *revised* 5 *September* 1994; *accepted* 9 *September* 1994)