Pergamon

Tetrahedron Letters, Vol. 36, No. 11, pp. 1913-1916, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00111-5

RING EXPANSION OF 2-CHLOROMETHYLBENZOTHIAZOLE : SYNTHESIS OF HETEROARYLALKYLIDENE 1,4-BENZOTHIAZINES

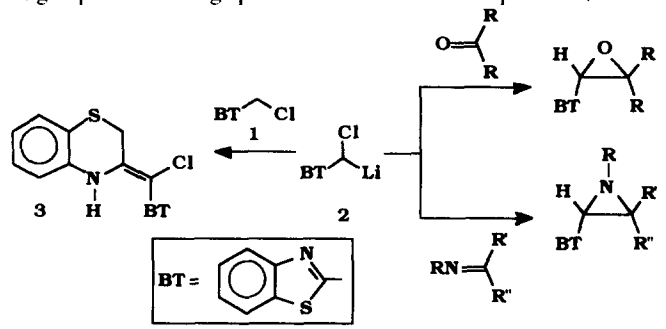
Saverio Florio*[a], Luigino Troisi[b] and Vito Capriati[a]

a) Dipartimento Farmaco-Chimico, Università, Via Orabona 4, 70125 - Bari, Italy;
b) Dipartimento di Biologia, Università, Via Monteroni, 73100 - Lecce, Italy.

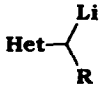
Abstract: the title heteroarylalkylidene dihydro-1,4-benzothiazines **7** have been prepared from heteroarylalkyllithiums **4** and 2-chloromethylbenzothiazole **1**.

We have recently reported that 2-benzothiazolylchloromethyllithium **2**, promptly available by lithiation of 2-chloromethylbenzothiazole (BTCH$_2$Cl) **1**, behaves as a halocarbenoid. Indeed, **2** adds to carbonyl compounds and imines to give benzothiazolyl oxiranes[1] and aziridines[2] respectively, and, in the absence of an external electrophile, adds to the C-N double bond of its precursor **1** causing an unusual thiazole-thiazine ring-expansion ending up with the formation of compound **3** (Scheme 1).[3]

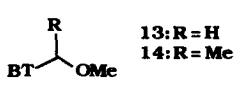
Scheme 1



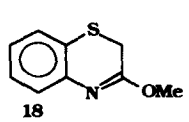
In the present communication we report on the synthetic exploitation of such a thiazole-thiazine ring-enlargement for the preparation of novel benzothiazine derivatives, a group of heterocyclic compounds which are especially interesting owing to their occurrence in nature as mammalian pigments and to their extensive pharmacological activity.[4-10]



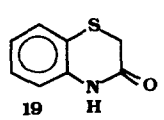
4a R = H; Het = 2-benzothiazolyl
4b R = Me; Het = 2-benzothiazolyl
4c R = Ph; Het = 2-benzothiazolyl
4d R = OMe; Het = 2-benzothiazolyl
4e R = H; Het = 2-pyridyl
4f R = H; Het = 2-quinolyl
4g R = H; Het = 2-pyrazinyl
4h R = H; Het = 3-pyridazinyl
4i R = H; Het = 2-(3-methyl)quinoxalinyl



13:R=H
14:R=Me



18

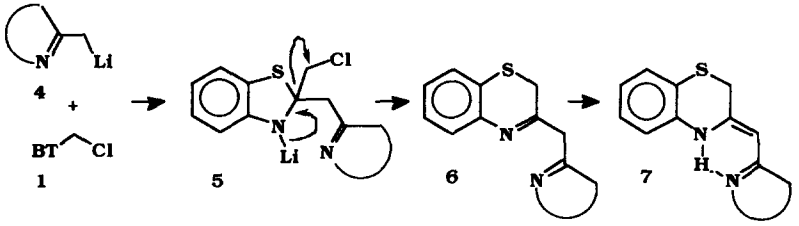


19

Treatment of 2-benzothiazolylmethyllithium **4a**, generated by lithiation (LDA) of commercial 2-methylbenzothiazole, with 2-chloromethylbenzothiazole **1** gave a very high yield of benzothiazine **7a** together with a small amount (~ 7%) of the substitution product **8a**. Similarly, the reaction of **1** with benzothiazolylethyllithium **4b** and benzothiazolylbenzyllithium **4c** furnished benzothiazines **7b** and **7c** accompanied by the substitution products **8b** and **8c**. Comparable results were obtained when **1** was treated with organolithiums prepared by lithiation of some other heteroarylmethanes. Indeed, treatment of **1** with pyridyl- **4e**, and quinolyl-methyllithium **4f** provided benzothiazines **7d** and **7e** and reactions with pyrazinyl- **4g**, pyridazinyl- **4h** and quinoxalinyl-methyllithium **4i** produced good yields of benzothiazines **7f**, **7g** and **7h** respectively (See Table).

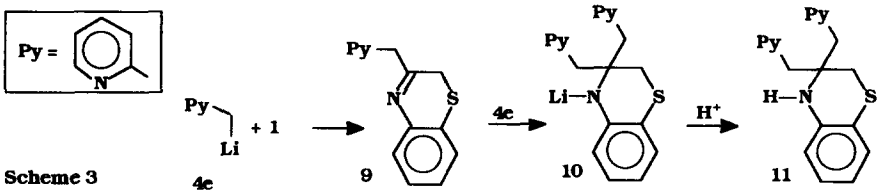
The formation of benzothiazines **7** could be rationalized by assuming that organolithiums **4** add to the C-N double bond of **1** to give thiazoline intermediates **5** which undergo ring-enlargement to the unstable dihydrobenzothiazines **6** and then to tautomers **7**, which are stabilized by the intramolecular hydrogen bond (Scheme 2).

Scheme 2



In the reaction of **1** with picolyllithium **4e** the formation of the dihydrobenzothiazine **11** was observed together with benzothiazine **7d**. A possible explanation is that organolithium **4e** adds to the ring-expanded compound **9** (or to its tautomer **7d**) leading to **10** and then to **11** (Scheme 3). Similarly, dihydrobenzothiazine **12** formed in the reaction of **1** with **4g**.

Scheme 3



Lithiation of 2-methoxymethylbenzothiazole **13** with LDA furnished **4d** that could be trapped with excess MeI yielding methoxyethylbenzothiazole **14**. Moreover, **4d** reacted with **13** and then with **1** to give a product which had the structure of **17**. For its formation, we suggest that lithiated ether **4d** adds to **13** giving thiazoline **15**, which undergoes ring opening with the leaving thiofinate being trapped by **1** to furnish **16**, which equilibrates to **17** (Scheme 4).

It was interesting to observe that also MeONa in methanol was capable of addition to the C-N double bond of **1**, thus initiating the thiazole-thiazine ring-enlargement. Indeed, when MeONa (5 eq.) was added to a methanol solution of **1** a 3.5:1:1 mixture (90% overall yield) of the substitution product **13** and the ring-expanded compounds **18** and **19** formed. Benzothiazinone **19** likely arises by the demethylation of methoxybenzothiazine **18**. It must be emphasized the unusual stability of **18**; indeed, this kind of benzothiazines are unstable and tend to dimerize.[11]

Scheme 4

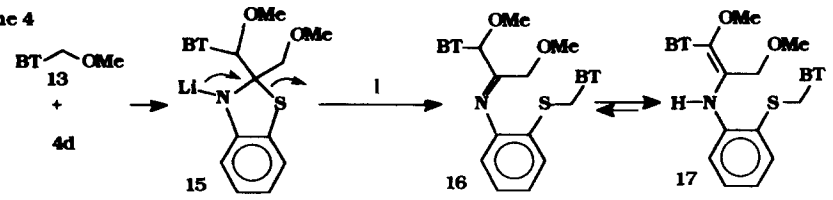
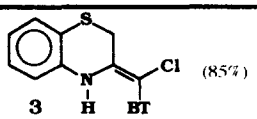
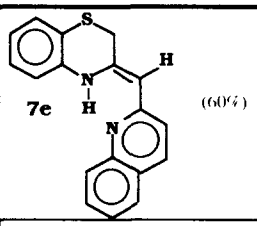
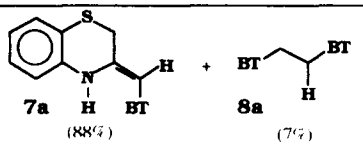
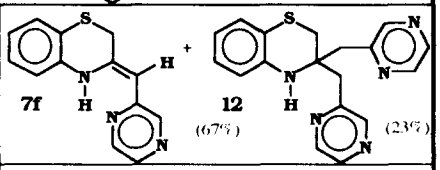
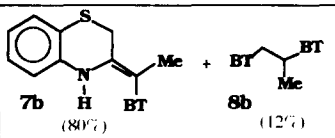
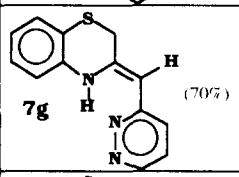
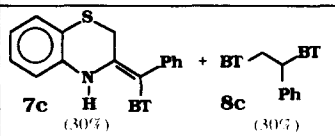
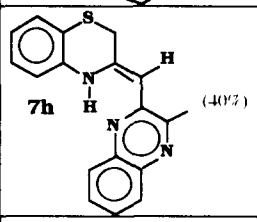
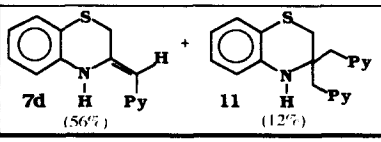


Table. Reaction of heteroarylalkyllithiums **2, 4a-i (RLi)** with 2-chloromethylbenzothiazole **1** in THF at -78°C.

RLi	Reaction Products (% yield)[a,b]	RLi	Reaction Products (% yield)[a,b]
2	 **3** (85%)	4f	 **7e** (60%)
4a	 **7a** (88%) **8a** (7%)	4g	 **7f** (67%) **12** (23%)
4b	 **7b** (80%) **8b** (12%)	4h	 **7g** (70%)
4c	 **7c** (30%) **8c** (30%)	4i	 **7h** (40%)
4e	 **7d** (56%) **11** (12%)		

a) Yields calculated on isolated, purified products. **b)** All the new benzothiazines showed consistent IR, ^{1}HNMR, ^{13}CNMR and MS data.

Alkylidene 1,4-benzothiazines **7a-h** appear to be quite stable.[12] This is likely due to the strong intramolecular hydrogen bond between the aza groups of the two heterocyclic systems. The low field resonance of the N-H proton in the ^{1}HNMR (δ: 12-13) is also consistent with a Z configuration at the

C-C double bond of the enamine system.[13] Support to this comes also from the value (5.3 Hz) of the $^{3}J(\underline{CH_2}C\underline{NH})$ coupling constant (^{13}CNMR) in the thiazine system.[14] The chelation properties of benzothiazines **7** are worthy to be evaluated as well as their potential in terms of phamacological activity.

Acknowledgements: We thank italian CNR and MURST (Rome) for financial support.

REFERENCES

1. Florio S. and Troisi L., *Tetrahedron Lett.*, **1992**, 33, 7953.
2. Florio S., Troisi L. and Capriati V., *J. Org. Chem.*, submitted.
3. Florio S., Capriati V., Solimini M.C. and Troisi L., *Tetrahedron Lett.*, **1994**, 35, 8481.
4. Kaiser C. and Setler P.E., in "*Burger's Medicinal Chemistry*" 4th ED.; Wolff M.E. Ed., Wiley, New York, **1980**, Part III, p.890; Prasad R.N., *ibid.*, **1969**, 12, 290; Gupta R.R., in "*Phenothiazines and Benzothiazines*", Elsevier, New York, **1988;** Brown C. and Davidson R.M., *Advances in Heterocyclic Chemistry*: 1,4-Benzothiazines, diihydro-1,4-benzothiazines and Related compounds, vol.38, Katritzky A.R., ed., Academic Press. Inc.,London, **1985** , p.135.
5. Krapcho J. and Turk C.F., *J.Med.Chem.*, **1973**, 16, 776; Millonig R.C., Goldlust M.B., Magnire W.E., Rubin B., Shulze E., Wojnar R.J. Turkheimer A.R., Schreiber W.F. and Brittain R.J., *ibid.*, **1973**, 16, 780.
6. Prasad R.N., *J.Med.Chem.*, **1969**, 12, 290.
7. Yematsu T., Hashimoto S. and Oshio H., *C.A.*, **1980**, 93, 46693b.
8. Hori M., Kataoka T., Shimizu H. and Ueda N., *Tetrahedron Lett.*, **1981**, 22, 1701; Trapani G., Reho A., Latrofa A., Morlacchi F. and Liso G., *J.Chem.Res (S)*, **1986**, 96.
9. Babudri F., Di Nunno L. and Florio S., *Synthesis*, **1982**, 488.
10. Babudri F., Di Nunno L. and Florio S., *Tetrahedron*, **1982**, 38, 3059; *Synthesis*, **1983**, 230.
11. Finar I. L.and Montgomery A. J., *J. Chem. Soc.*, **1961**, 367.
12. **General Procedure:** To diisopropylamine (2.4 mmole) in 10 ml of THF was added at 0°C 1ml of 2.4N n-BuLi. To this solution, cooled at -78°C, was added dropwise a solution of **4a** (2.0 mmole) in 10 ml of THF. After 15 min at -78°C a THF solution of **1** (2.0 mmole) was added dropwise and then the reaction mixture was allowed to warm to RT and quenched with aqueous NH_4Cl after 6h. Extraction with ether (3x25 ml), drying over Na_2SO_4 and evaporation of the solvent under reduced pressure left a residue that was column chromatographed (silica gel, E.P./E.E.:7/3 as eluent) to give benzothiazine **7a.**
13. Marchini P., Trapani G., Liso G. and Berardi V., *Phosphorous Sulfur*, **1977**, 3, 309; Trapani G., Reho A., Latrofa A., Morlacchi F. and Liso G., *Heterocycles*, **1985**, 23, 1619.
14. Bundgaard T., Jacobsen H.J. and Rahkamaa E.J., *J.Magn.Res.*, **1975**, 19, 345; Sopchik A. E. and Kingsbury C. H., *J.Chem.Soc.Perk II*, **1979**, 1058.

(*Received in UK* 22 *December* 1994; *accepted* 13 *January* 1995)