Oxidative Ring-Expansion of Benzothiazolines into 1,4-Benzothiazines

Gaetano Liso, Giuseppe Trapani, Andrea Latrofa and Paolo Marchini

Istituto di Chimica Organica della Facoltà di Farmacia, Università di Bari, 70126 Bari, Italy

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By treatment in boiling DMSO, benzothiazolines **1** yield 1,4-benzothiazines **4** in some cases together with benzothiazoles. Two competing pathways, namely oxidative ring-expansion and decomposition of benzothiazoline accounting for the formation of **4** and benzothiazoles, respectively, are suggested.

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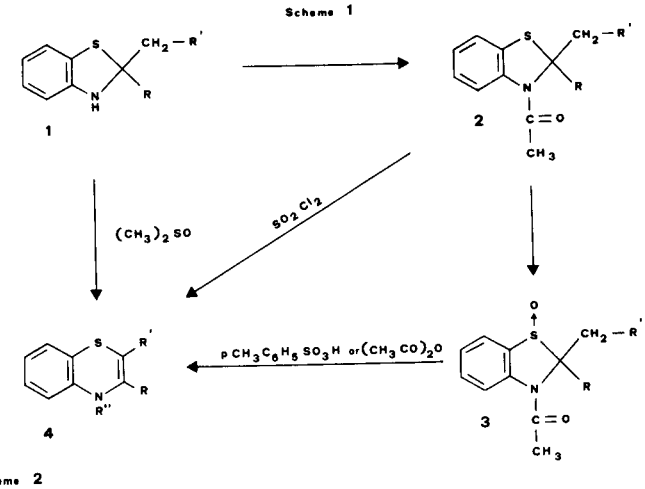
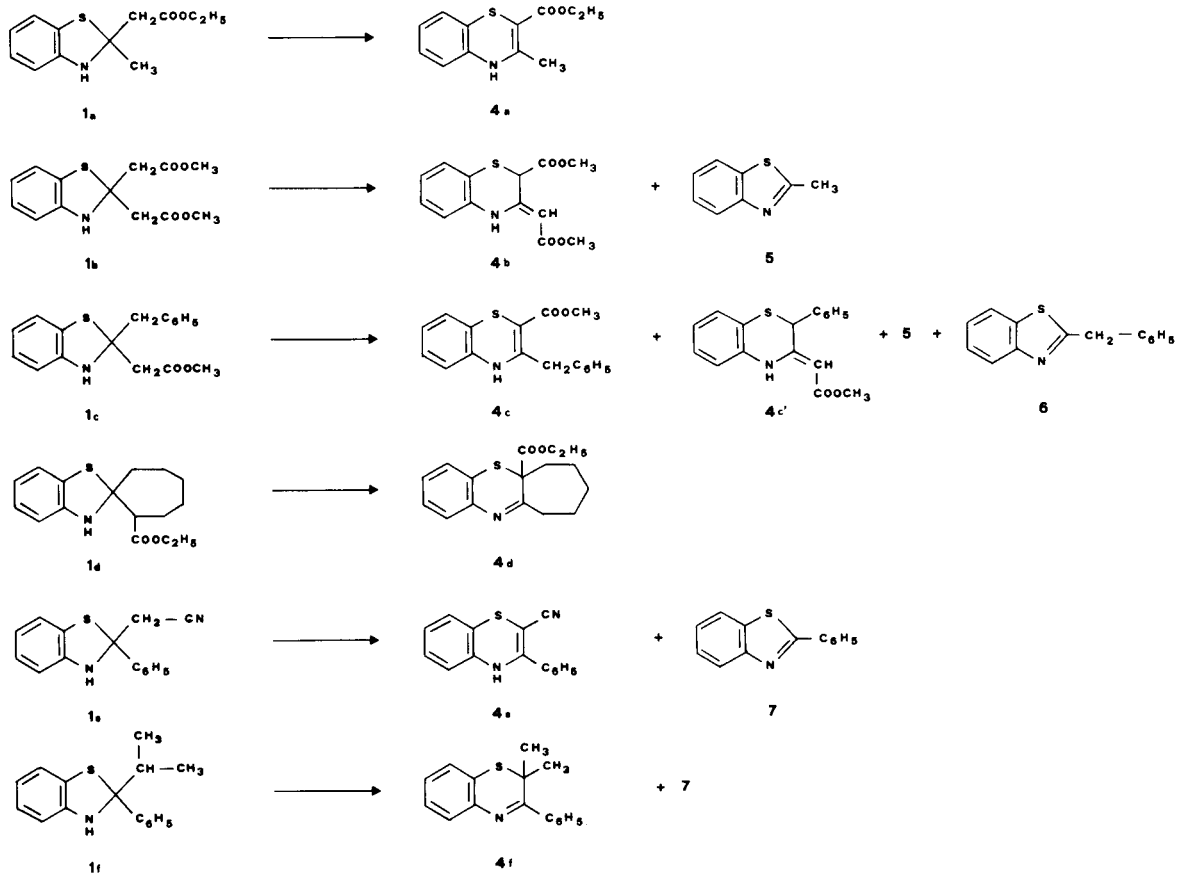
Interest has recently arisen in the ring-expansion of benzothiazolines into 1,4-benzothiazines. As summarized in Scheme 1, the formation of 1,4-benzothiazines **4** (R″ = $COCH_3$) has been achieved starting from *N*-acylbenzothiazolines **2**, both by reaction with sulfuryl chloride (1) and by treatment of the corresponding S→O derivatives **3** with *p*-toluenesulfonic acid or acetic anhydride (2). Furthermore, only one example of direct conversion of *N*-unsubstituted benzothiazoline **1** (R = H, R′ = $COOC_2H_5$) into 1,4-benzothiazine **4** (R = R″ = H, R′ = $COOC_2H_5$) has been found to occur in boiling dimethyl sulfoxide (DMSO) (3).

Scheme 1



In an attempt to explore the feasibility of ring-expanding 2,2-disubstituted benzothiazolines by this lat-

Scheme 2



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ter way and to provide further insight into the possible reaction pathway, a number of appropriately substituted benzothiazolines were prepared and a study made of their behaviour in boiling DMSO.

The required dialkyl (**1a-c**), cycloalkyl (**1d**), alkyl-aryl (**1e,f**) benzothiazolines (Scheme 2) were conveniently prepared by the acid-catalyzed reaction between 2-aminothiophenol and the appropriate ketone (4); analytical and spectral data for the new compounds **1e,f** are reported in the experimental section.

As summarized in Scheme 2, by boiling a DMSO solution of benzothiazolines **1** the 1,4-benzothiazines **4** were obtained in moderate yields (21-46%) in any case. In particular, the compound **1a** yielded exclusively the corresponding 1,4-benzothiazine **4a**. Compound **1b** led to 1,4-benzothiazine **4b** and to 2-methyl benzothiazole **5**. Compound **1c** afforded a complex reaction mixture: isomer 1,4-benzothiazines **4c,c'**, 2-benzylbenzothiazole **6** and compound **5**. From **1d**, 1,4-benzothiazine **4d**, together with some unidentified products, was obtained. In the cases **1e,f**, the corresponding 1,4-benzothiazines **4e,f**, together with 2-phenylbenzothiazole **7**, were isolated.

The structures of **4a-f**, **5**, **6** and **7** were confirmed by comparison with authentic samples prepared according to the literature (5,6).

It is interesting to point out that compound **4c** does not isomerize to **4c'** in boiling DMSO (7). Therefore the two isomer 1,4-benzothiazines **4c** and **4c'** arise from the ring-expansion in the two possible directions of compound **1c**. In this connection, also benzothiazolines **1a,d** could ring-expand in two directions. However, in these two cases, the isolated products **4a,d** indicate that expansion occurs only in the direction of the more substituted carbon atom.

The formation of 2-substituted benzothiazoles with the concurrent elimination of alkane, by thermal decomposition of the benzothiazolines, is known (8) (equation 1 in Scheme 3). In this context, benzothiazoles **6** and **7** were expected while the formation of 2-methyl benzothiazole **5**, from **1b,c** instead of methyl 2-benzothiazolyl acetate **8**, appeared at first glance to be abnormal (9). However, due to the fact that compound **8** was quantitatively converted into **5** in boiling DMSO it is confidently suggested that **8** is an intermediate of **5** in the decomposition of **1b,c**. A possible rationalization of this result is shown in Scheme 3 (equation 2) and involves the facile thermal decarboxylation of acid **9** (10) arising from hydrolysis of **8** (11).

While the results so far available can hardly be regarded as conclusive, we feel that our experimental data indicate that benzothiazolines, in boiling DMSO, may undergo two competing reactions, namely decomposition and oxidative ring-expansion to give 2-substituted benzothiazoles or 2,3-disubstituted 1,4-benzothiazines, respectively. Mechanistically, the oxidative ring-expansion reaction could be rationalized by invoking the intermediacy of an enamine species **11** (Scheme 4) which cyclizes to give products such as **4**. Such an intermediate should arise by reaction between DMSO and a ring-opened thiol species such as **10**, as hypothesized for the reaction between DMSO and thiol compounds (12). Alternatively, intermediate **11**, by reaction with **10**, could give the bis-enamine disulfide species **12** (12) which in turn would yield compounds **4** and **1** (13).

The oxidative ring-expansion reaction described in the present note represents a new and direct route to 1,4-benzothiazines by conversion of benzothiazolines, which are readily accessible compounds by conventional methods (4). Studies to optimize the oxidative ring-expansion reaction are under way.

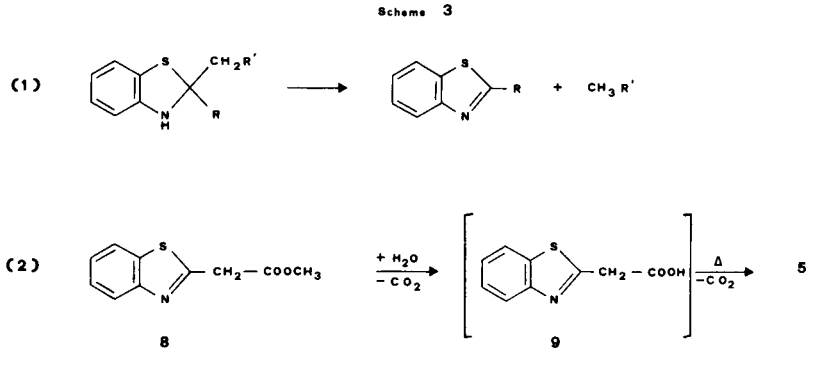
EXPERIMENTAL

Melting points are uncorrected. Infrared spectra as nujol mulls were obtained on a Perkin-Elmer Model 257; proton magnetic resonance spectra were determined with a Varian EM-360A spectrometer, using tetramethylsilane as an internal standard. All m/e values determined on a Perkin-Elmer Model 270 low-resolution mass spectrometer. All reactions were performed under nitrogen. Column chromatography was performed on silica gel (Merck 70-325 mesh) using petroleum ether:ethyl acetate 9:1 as eluent.

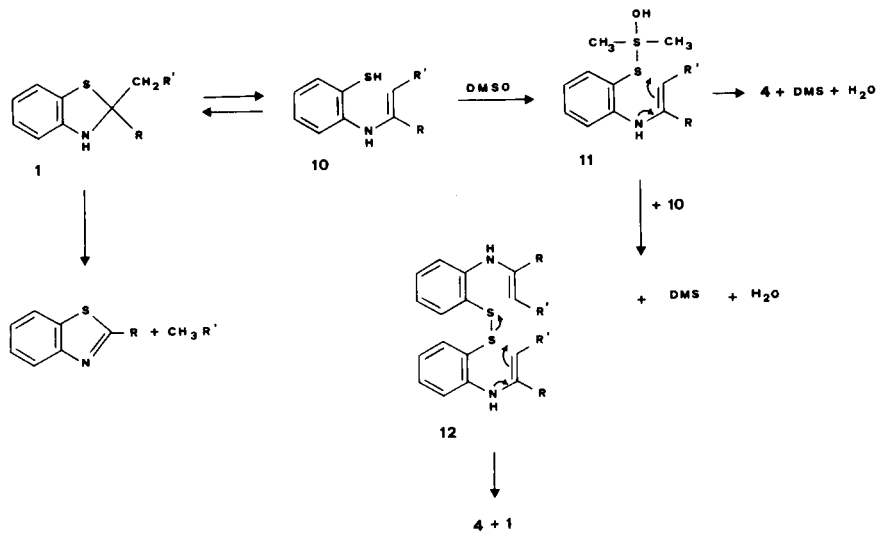
Preparation of the Benzothiazolines **1e,f** (14).

In agreement with the general standard method for the synthesis of benzothiazolines (4), equimolar amounts of 2-aminothiophenol and the appropriate ketone (0.01 mole) were refluxed, under nitrogen, for 15 hours in toluene (75 ml.) containing catalytic amounts of *p*-toluene-

Scheme 3



Scheme 4



sulfonic acid. The cooled solution was washed with 10% potassium carbonate solution, dried over sodium sulfate, and evaporated. Column chromatography of the residue gave the benzothiazolines **1e,f**.

2-Cyanomethyl-2-phenyl-2,3-dihydro-1,3-benzothiazole (**1e**).

This compound was obtained in a yield of 42%, m.p. 98-99° (from 2-propanol); ir: cm^{-1} 3380 (NH), 2240 (CN); nmr (deuteriochloroform): δ 7.90-6.60 (m, 9H, aromatic), 4.85 (s, 1H, NH), 3.38 (s, 2H, CH_2); ms: 252 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.58; H, 4.80; N, 11.13.

2-Isopropyl-2-phenyl-2,3-dihydro-1,3-benzothiazole (**1f**).

This compound was obtained in a yield of 44% as a colorless oil which solidified on standing, at room temperature, m.p. 63-64°; ir: cm^{-1} 3380 (NH); nmr (deuteriochloroform): δ 7.72-6.48 (m, 9H, aromatic), 4.10 (s, 1H, NH), 2.70 (m, 1H, CH), 1.08 (d, 3H, CH_3), 0.95 (d, 3H, CH_3); ms: 255 (M^+).

Anal. Calcd. for $C_{16}H_{17}NS$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.18; H, 6.73; N, 5.55.

General Procedure for the Reaction in Dimethyl Sulfoxide.

A solution of **1** (5 mmoles) in dimethyl sulfoxide (15 ml.) was refluxed for 3 hours in the cases **1a-d**, and 0.5 and 8 hours in the cases **1e** and **1f**, respectively. The solution, when cold, was poured in water and extracted with chloroform. The organic layer, washed with water, was dried over anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography.

2-Ethoxycarbonyl-3-methyl-4*H*-benzo[*b*][1,4]thiazine (**4a**).

This compound was obtained in a yield of 33% (50% based on benzothiazoline compound consumed), m.p. 147° (from ethanol) [lit. (5a) m.p. 146-147°].

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.21; H, 5.68; N, 5.85.

2-Methoxycarbonyl-3-methoxycarbonylmethylene-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine (**4b**).

This compound was obtained in a yield of 21% (27% based on benzothiazoline compound consumed), m.p. 114-116° (from ethanol) [lit. (5a) m.p. 114-116°].

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.91; H, 4.70; N, 5.02. Found: C, 55.78; H, 4.57; N, 5.00.

2-Methylbenzothiazole (**5**) was obtained in a yield of 13% (18% based on benzothiazoline compound consumed) in addition to **4b**, by the method described for **4b**.

3-Benzyl-2-methoxycarbonyl-4*H*-benzo[*b*][1,4]thiazine (**4c**).

This compound was obtained in a yield of 16%, m.p. 135° (from ethanol) [lit. (5a) m.p. 133-135°].

Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.70; H, 5.15; N, 4.68.

3-Methoxycarbonylmethylene-2-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine (**4c'**).

This compound was obtained in a yield of 8%, m.p. 110° (from ethanol) [lit. (5a) m.p. 110-111°].

Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.65; H, 5.10; N, 4.73.

2-Methylbenzothiazole **5** and 2-benzylbenzothiazole **6** were obtained in a yield of 44% and 15%, respectively in addition to **4c** and **4c'** by the method described for **4c** and **4c'**.

5a-Ethoxycarbonyl-5a,6,7,8,9,10-hexahydrobenzo[*b*]cycloepta[*e*][1,4]thiazine (**4d**).

This compound was obtained in a yield of 21%, m.p. 57-59° (from 2-propanol) [lit. (5b) m.p. 57-59°].

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84. Found: C, 66.61; H, 6.71; N, 4.57.

2-Cyano-3-phenyl-4*H*-benzo[*b*][1,4]thiazine (**4e**).

This compound was obtained in a yield of 32%, m.p. 211° (from 2-propanol) [lit. (3) m.p. 211°].

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.99; H, 4.03; N, 11.20. Found: C, 72.01; H, 4.05; N, 11.20.

2-Phenyl benzothiazole **7** was obtained in a yield of 46% in addition to **4e** by the method described for **4e**.

2,2-Dimethyl-3-phenyl-2*H*-benzo[*b*][1,4]thiazine (**4f**).

This compound was obtained in a yield of 46%, m.p. 93-94° (from ethanol) [lit. (5c) m.p. 93-94°].

Anal. Calcd. for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53. Found: C, 75.91; H, 6.02; N, 5.49.

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