Reaction Between 2,2′-Dithiodianiline and Acetylenic Ketones or Esters. A New Synthesis of 4*H*-1,4-Benzothiazines

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The title compounds (**3a-c**) together with the benzothiazolines (**4b-c**) were obtained by reaction between 2,2′-dithiodianiline (**1**) and acetylenic ketone (**2a**) or esters (**2b-c**). A possible pathway involving the formation and subsequent cyclization to **3** of enamine intermediates **A** and/or **B**, is suggested.

J. Heterocyclic Chem., **17**, 377 (1980).

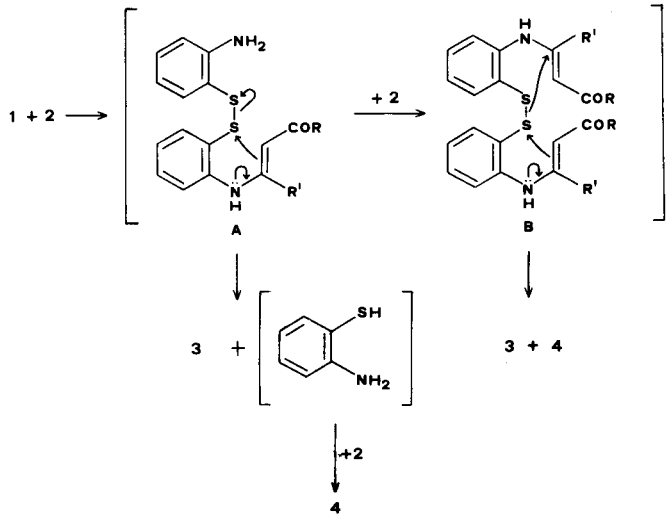
In connection with a project involving the synthesis of 1,4-benzothiazine derivatives for biological evaluation, we needed 2-acetyl-3-phenyl-4*H*-benzo[*b*][1,4]thiazine (**3a**) (1). After an exhaustive literature search it appeared that none of the reported synthetic methods (2) would be useful for our purpose.

We now wish to report that **3a** has been obtained in satisfactory yield (65%) by refluxing an ethanolic solution of 2,2′-dithiodioaniline (**1**) and 4-phenyl-3-butyn-2-one (**2a**) in a molar ratio of 1:2. The crude red precipitate was shown to be homogeneous by thin-layer chromatographic analysis. Its nmr spectrum (acetone-d_6) showed a broad signal at δ 7.94 (1H,NH), a singlet at δ 7.48 (5H, aromatic), a multiplet between δ 7.70 and 6.60 (4H, aromatic), a singlet at δ 1.48 (3H,CH_3). Moreover the presence in the mass spectrum of the base peak at m/e 224, corresponding to the loss of CH_3CO moiety from the parent peak (m/e 267), confirms unambiguously the structure of **3a** (3).

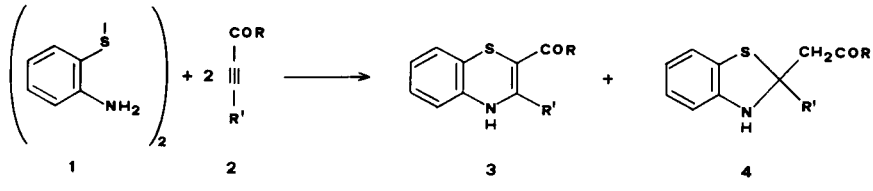
The formation of **3a** by this new synthetic approach, induced us to extend the reaction to other acetylenic substrates such as dimethyl acetylenedicarboxylate and ethyl propiolate. In these last cases the expected 1,4-benzothiazine **3** was obtained in very good yield (86-90%) together with the benzothiazoline **4**. Furthermore we have found that **3** and **4** are formed in almost equimolar ratio according to the reported equation in the Scheme 1.

A possible pathway accounting for the formation of **3** and **4** is shown in the Scheme 2 and involves the cyclization to **3** of enaminic intermediates **A** (4) and/or **B** by scission of the sulfur-sulfur bond upon attack by nucleophilic enamine system. It is worth noting that the cycylization of intermediate **A** would lead to the formation of 2-aminothiophenol as by product, thus the benzothiazoline **4**

Scheme 2



Scheme 1



*a) R = CH_3 R' = C_6H_5
b) R = OCH_3 R' = $COOCH_3$
c) R = OC_2H_5 R' = H

*In this case was not investigated if **4a** formation occurs.

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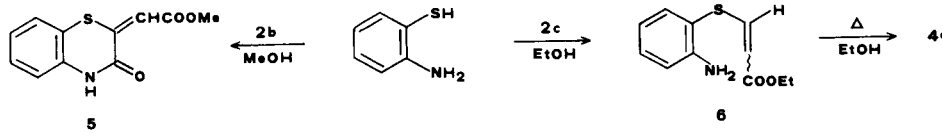
Table

Compound	M.p. (Solvent of crystallization) and/or B.p. (Torr)	Ir (a) (cm^{-1}) N-H	C=O	C=C	Nmr (b) (δ)
3a	177° (2-propanol)	3200	1580	1560	7.94 (s, 1H, NH); 7.48 (s, 5H, aromatic); 7.70-6.60 (m, 4H, aromatic), 1.48 (s, 3H, CH_3).
3b	110° (2-propanol)	3325	1740 1690	1615	8.1 (s, 1H, NH); 6.50-7.00 (m, 4H, aromatic); 3.71 and 3.62 (2s, 3H each, 2 CH_3).
4b	98° (2-propanol)	3310	1750 1720		7.00-6.52 (m, 4H, aromatic); 5.25 (s, 1H, NH); 3.72 and 3.68 (2s, 3H each, 2 CH_3); 3.30 (dd, 2H, CH_2CO).
4c	82-84° (0.015)	3320	1740		7.00-6.45 (m, 4H, aromatic); 5.40 (X part of ABX system, 1H, CH); 4.70 (s, 1H, NH); 4.10 (q, 2H, CH_2O); 2.90 (AB part, 2H, CH_2); 1.22 (t, 3H, CH_3).
6 (c)		3440 3345	1710	1625	7.54 (d, 0.13H, vinylic J = 15 cps); 7.40-6.60 (m, 4H, aromatic + d, 0.87 H vinylic at 6.92 J = 10 cps); 5.86 (d, 0.87H, vinylic J = 10 cps); 5.39 (d, 0.13H, vinylic J = 15 cps); 4.50-3.80 (q + s, 4H, CH_2O + NH_2); 1.34 (t, 3H, CH_3).

(a) Compound **4c** and **6** as liquid film, the others in nujol mull. (b) Nmr spectra of **3a** and **3b** recorded in acetone-d_6, for the others deuteriochloroform was used. (c) *Cis/trans* mixture 87:13.

Scheme 3



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would be successively originate by reaction of thiol with alkyne **2**.

We believe that this last pathway could be excluded at least in the case of **2b** since from the reaction of 2-aminothiophenol with alkyne **2b** the lactam **5** (5) was obtained, while using **2c** the corresponding benzothiazoline **4c** was quantitatively formed *via* the vinyl thioether intermediate **6** (Scheme 3).

Physical data of new compounds are reported in the table.

Further studies are in progress in order to show the scope and limitations of this reaction which provides a facile one-step route to some 1,4-benzothiazines, otherwise difficult to obtain.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 257; proton magnetic resonance spectra were determined with a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard. All m/e values were determined on Perkin-Elmer Model 270 low-resolution mass spectrometer. Column chromatography was performed on silica gel (Merck 70-235 mesh) using petroleum ether:ethyl acetate, 85:15 as eluent.

The yields are based on 2,2′-dithiodianiline used.

Reaction of 2,2′-Dithiodianiline with Alkynes **2**.

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

A solution of **1** (0.01 mole) and **2a** (0.02 mole) in ethanol (50 ml.) was refluxed under nitrogen for 7 hours. After cooling, the resulting red precipitate **3a** was collected by filtration (1.1 g.) and partial evaporation of the solvent under vacuum afforded additional **3a** (0.6 g.), yield 65%.

Anal. Calcd. for $C_{16}H_{13}NOS$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.64; H, 4.78; N, 5.22.

2-Methoxycarbonylmethyl-2-methoxycarbonylbenzothiazoline (**4b**).

A solution of **1** (0.01 mole) and **2b** (0.02 mole) in ethanol (70 ml.) was refluxed under nitrogen for 3 hours. Evaporation of the solvent and column chromatography of the residue gave **4b** in 87% yield.

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.93; H, 4.90; N, 5.24. Found: C, 54.01; H, 4.77; N, 5.01.

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

This compound was obtained in a yield of 86% in addition to **4b** by the method described above for **4b**.

Anal. Calcd. for $C_{12}H_{11}NO_4S$: C, 54.34; H, 4.18; N, 5.28. Found: C, 54.10; H, 4.01; N, 5.10.

2-Ethoxcarbonylmethylbenzothiazoline (**4c**).

A solution of **1** (0.01 mole) and **2c** (0.02 mole) in ethanol (70 ml.) was heated in a sealed tube at 120° for 8 hours. Evaporation of the solvent and column chromatography of the residue gave **4c** in a yield of 86%.

Anal. Calcd. for $C_{11}H_{13}NO_2S$: C, 59.18; H, 5.81; N, 6.28. Found: C, 59.01; H, 5.77; N, 6.25.

2-Ethoxycarbonyl-4*H*-benzo[*b*][1,4]thiazine (**3c**) (6).

This compound was obtained in a yield of 90% in addition to **4c** by the method described for **4c**.

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.76; H, 5.10; N, 6.27.

Reaction of 2-Aminothiophenol with **2c**.

2-Aminothiophenol (0.01 mole) and **2c** (0.01 mole) in absolute ethanol (10 ml.) were allowed to react. After 30 minutes the solvent was evaporated under vacuum at room temperature and the crude adduct **6** (100% yield) was obtained as a pale yellow oil. The nmr spectrum of **6** showed the presence of the *cis/trans* vinyl thioether in the molar ratio of 87:13.

Cyclization of **6** to **4c**.

On heating an ethanolic solution of **6** at 120° in a sealed tube for 8 hours, **4c** was obtained quantitatively.

Acknowledgement.

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REFERENCES AND NOTES

(1) Some dihydro derivatives of **3a** were shown to be a new interesting class of antiinflammatory agents; J. Krapcho and C. F. Turk, *J. Med. Chem.*, **16**, 766 (1973).

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(3) Similarly the mass spectrum of 2-benzoyl-3-methyl-4*H*-benzo[*b*]-[1,4]thiazine, obtained according to procedures (2a-b), shows a peak at m/e 162 corresponding to the loss of C_6H_5CO moiety from the parent peak at 267.

(4) The intermediate **A**, which would yield **3** and 2-aminothiophenol have been also hypothized for the reaction between **1** and β ketoesters: P. Marchini, G. Trapani, G. Liso, V. Berardi, F. Liberatori and F. M. Moracci, *Phosphorous and Sulfur*, **2**, 109 (1976).

(5) S. M. Kalbag, M. D. Nair, P. Rajagopalan and C. N. Talaty, *Tetrahedron*, **23**, 1911 (1967).

(6) Physical data of **3c** are in agreement with those reported by G. Scapini, F. Duro and G. Pappalardo, *Ann. Chim. (Rome)* **58**, 1058 (1968).