Adducts of 2-Aminothiophenol with Acetylenic Nitriles or Esters and their Conversion into Benzothiazoles and/or 1,4-Benzothiazines

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The reaction between 2-aminothiophenol **1** and acetylenic nitriles or esters **2a-d** leads to the vinyl thioethers **3a-d**. The conversion of **3** into benzothiazoles **8** and/or 1,4-benzothiazines **9**, in boiling dimethyl sulfoxide, has been achieved. A possible pathway involving benzothiazolines **5** as key intermediates is suggested.

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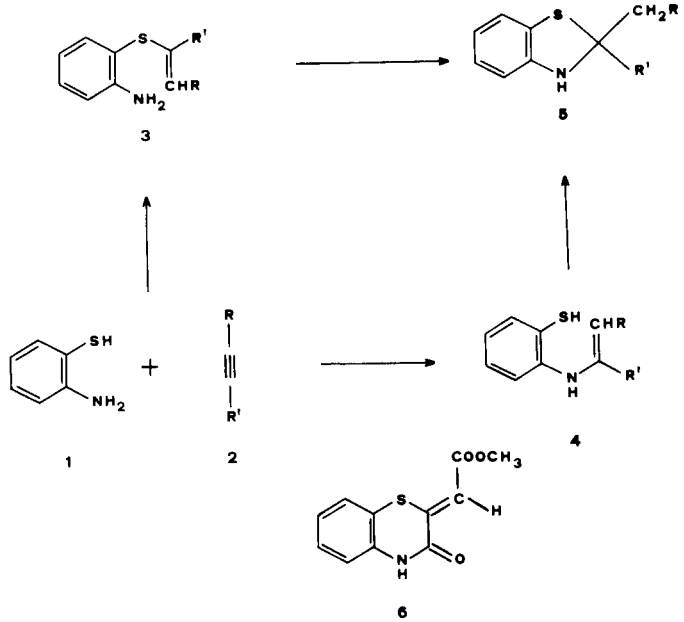
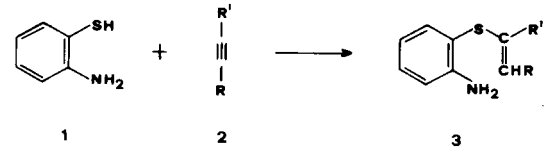
In connection with our previous report (1) on the reaction between 2,2'-dithiodianiline and acetylenic compounds, it was of interest to ascertain which benzothiazolines **5** could arise by cyclization of vinyl thioether **3** and/or enaminothiol compound **4** hypothesized intermediates (Scheme 1). Therefore, the synthesis of **3** and **4** was attempted.

Scheme 1



Examination of the literature shows that compounds **3** [R = PPh_3^+, R' = Ph (2); R = COOH, R' = H (3); R = COOEt, R' = H (1); R = R' = COPh (4)] and **4** [R = CN, R' = Ph (5)] have been obtained by the addition of the bifunctional nucleophile 2-aminothiophenol **1** to related alkynes **2**. Further, in the case of dimethylacetylenedicarboxylate (DMAD), neither isomer was isolated, but rather only the (*Z*)-2-methoxycarbonylmethylene-3,4-dihydro-3-oxo-2*H*-benzo-1,4-thiazine **6** was obtained (6). Only compound **3** (R = COOEt, R' = H) has been found to lead to the corresponding benzothiazoline **5** (R = COOEt, R' = H) (1).

Scheme 2



a) R = R' = $COOCH_3$

b) R = $COOC_2H_5$ R' = C_6H_5

c) R = CN R' = C_6H_5

*d) R = $COOC_2H_5$ R' = H

*This case has been previously reported (1).

Accordingly, we have reacted **1** with alkynes **2a-c** (Scheme 2). In every case the vinyl thioethers **3a-c** were obtained. Thus, it has been found that the thiol group reacts first in the addition reaction of **1** to **2c** (7), in contrast with results reported by Fomum, *et al.* (5). In particular, while equimolar amounts of **1** and **2b,c** react, under nitrogen, to yield the vinyl thioethers **3b-c** as (*E,Z*)-mixtures, the reaction of **2a** gives (*E*)-**3a** together with **6**, resulting from (*Z*)-**3a** isomer cyclization (6). The structures of compounds **3** are fully supported by microanalytical data, molecular weight and spectral data; in particular all ir spectra show two absorption bands in the region 3480-3360 cm^{-1}, clearly due to the primary amino group. Physical and spectral data are reported in Table 1.

Nmr spectroscopy was used in the configurational assignment of compounds **3b-d**; **3a** must exist in the (*E*)-form since the (*Z*)-**3a** form yields **6** (6). The signal relative to the vinyl protons of **3d** at lower field (Table 2) has been assigned to the proton which is β to the R group in both stereoisomers, comparing δ values reported for related vinyl thioethers (9), as well as for the vicinal proton coupling (10). Moreover, the identity of chemical shift δ values found for (*E*)-**3a** H_α (δ 5.38) and (*E*)-**3d** H_α (δ 5.39) (Table 2) further supports these assignments, since no shielding effect is produced by the carboxylalkyl substituent *trans* to the H_α proton in similar substituted ethylenes (11).

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Table 1

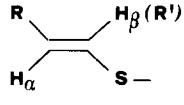
Physical and Spectral Data of Compounds **3**

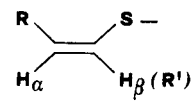
Compound No.	Yield %	M.p.	Ir (a) (cm^{-1}) N-H	C≡N	C=O	C=C	Nmr (δ) Deuteriochloroform	Ms (M^+)
(*E*)-**3a**	13	oil	3480 3380		1730	1620	7.40-6.60 (m, 4H, aromatic), 5.38 (s, 1H, vinylic), 4.35 (s, 2H, NH_2), 3.78 (s, 3H, CH_3), 3.65 (s, 3H, CH_3)	267
(*E*)-**3b**	23	113° (b)	3480 3380		1710	1610	7.50-6.60 (m, 9H, aromatic), 5.30 (s, 1H, vinylic), 4.20-3.60 (q + s, 4H, CH_2O + NH_2), 1.00 (t, 3H, CH_3)	299
(*Z*)-**3b**	56	oil	3460 3360		1690	1610	7.30-6.26 (m, 9H, aromatic), 6.09 (s, 1H, vinylic), 4.44-4.00 (q + s, 4H, CH_2O + NH_2), 1.31 (t, 3H, CH_3)	299
(*E,Z*)-**3c**	97	oil	3440 3360	2200		1610	7.80-6.40 (m, 9H, aromatic), 5.58 (s, 0.62H, vinylic), 4.73 (s, 0.38H, vinylic), 4.40-4.10 (two broad signals, 2H, NH_2)	252

(a) The oils were determined as liquid films while the other compounds were recorded in a nujol mull. (b) Solvent of crystallization was 2-propanol.

Table 2

Assignement of vinyl proton resonances in compounds **3** (a)





Compounds	R	R'	δ_{H_α}	δ_{H_β}	δ_{H_α}	δ_{H_β}
3a	$COOCH_3$	$COOCH_3$	5.38			
3b	$COOC_2H_5$	C_6H_5	5.30 (5.33 ±0.12)		6.09 (6.25 ±0.08)	
3c	CN	C_6H_5	4.73 (4.84 ±0.12)		5.58 (5.68 ±0.08)	
3d	$COOC_2H_5$	H	5.39(b)	7.54(b)	5.86(c)	6.92(c)

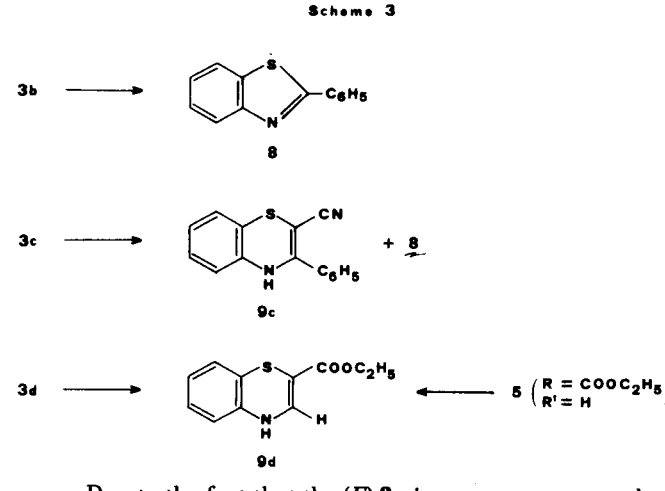
(a) Data in parenthesis have been calculated according to Tobey's method (12). (b) $J_{H_\alpha H_\beta}$ =15cps. (c) $J_{H_\alpha H_\beta}$ =10cps.

Furthermore, having determined the configuration for the isomers of **3d**, it is possible to calculate, according to Tobey's method (12), δ nmr values for isomers of **3b**, since the magnitude of the nmr shielding effect produced by a phenyl substituent *trans* or *cis* to the H_α proton is known (-0.06 ± 0.12 and $+0.39 \pm 0.08$ ppm, respectively) (12). Similarly, the H_α vinyl proton resonances for the isomers of **3c** have been calculated by using the reported (9) H_α chemical shifts of 3-(*p*-tolylthio)prop-2-enenitrile (**7**).

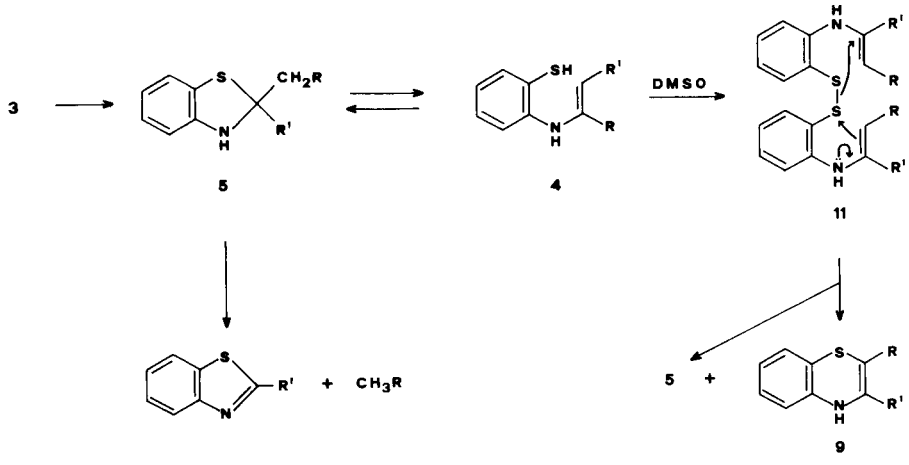
The good agreement found between the observed and calculated nmr δ values for the vinyl protons of **3b** and **3c** (Table 2) confidently supports the structural assignments made.

We have previously reported (1) that benzothiazoline **5** (R = R' = $COOCH_3$), obtained by the reaction between 2,2'-dithiodianiline and DMAD in boiling methanol, should form *via* the enamino thiol intermediate and not *via* the vinyl thioether isomer, since the reaction between **1** and **2a** is known to lead to **6**. Now, having (*E*)-**3a** in our hands, it was necessary to ascertain if its cyclization could occur. Due to the fact that the (*E*)-**3a** isomer was recovered unchanged by treatment in boiling methanol, and since the chemical behaviour of the (*Z*)-**3a** isomer is known, we can exlcude that **5** (R = R' = $COOCH_3$) may form in the cyclization of vinyl thioether **3a**.

Scheme 3



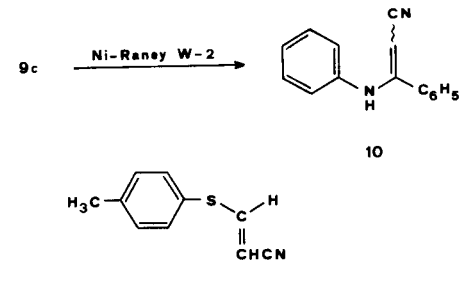
Scheme 4



In a further attempt to cyclize compounds **3b-d** in boiling dimethyl sulfoxide we have obtained benzothiazole **8** and/or 1,4-benzothiazine **9**, depending on the substrate (Scheme 3). Furthermore, under the same conditions the benzothiazoline **5** (R = $COOC_2H_5$, R′ = H) (1) was converted in high yield (82%) to 1,4-benzothiazine **9d**.

The structure of the new compound 2-cyano-3-phenyl-4*H*-benzo[*b*][1,4]thiazine (**9c**) is supported fully by comparison with a sample prepared by a standard method (13), as well as by its desulfurization product 3-anilino-3-phenylprop-2-enenitrile (**10**). The formation of compounds **8** and **9** can be explained by assuming the benzothiazoline **5** as a key intermediate (Scheme 4) for the following reasons: (a) the benzothiazoline **5** (R = $COOC_2H_5$, R′ = H), obtained by cyclization of **3d** (1) in boiling dimethyl sulfoxide leads to 1,4-benzothiazine **9d**; (b) the thermal conversion of benzothiazolines into benzothiazoles is well known (14); (c) ring-chain tautomeric equilibria between the benzothiazoline and the enaminothiol form **4** is also known (15), as well as oxidation by dimethyl sulfoxide of thiols to disulfide (16); (d) the *bis*-enaminic intermediate **11**, which would yield benzothiazoline and 1,4-benzothiazine, has previously been hypothesized by us (1).

Further investigation is underway in order to study the influence of the substituents of the benzothiazoline system on this new oxidative ring enlargement of benzothiazoline to 1,4-benzothiazine (17).



EXPERIMENTAL

Melting 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 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. Preparative thin-layer chromatography (tlc) was performed on Merck PF_{254} silica gel coated plates using petroleum ether:ethyl acetate 9:1 as eluent.

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

(*E*)-Dimethyl 1-(2-Aminophenylthio)ethylene-1,2-dicarboxylate (*E*-**3a**).

A solution of **1** (0.01 mole) and **2a** (0.01 mole) in methanol (20 ml.) was allowed to react, at room temperature under stirring. After 2 hours the resulting mixture was then filtered to remove compound **6** (86% yield), m.p. 270° [lit. (6) m.p. 270°], and the filtrate was evaporated. Column chromatography of the residue gave (*E*)-**3a** in 13% yield.

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.64; H, 4.70; N, 4.96.

(*E*)-Ethyl 1-(2-Aminophenylthio)-1-phenylethylene-2-carboxylate (*E*-**3b**).

A solution of **1** (0.01 mole) and **2b** (0.01 mole) in ethanol (40 ml.) was refluxed for 8 hours. Evaporation of the solvent and column chromatography of the residue gave (*E*)-**3b** in 23% yield.

Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.04; H, 5.88; N, 4.81.

(*Z*)-Ethyl 1-(2-Aminophenylthio)-1-phenylethylene-2-carboxylate (*Z*-**3b**).

This compound was obtained in 56% yield in addition to (*E*)-**3b** by the method described for (*E*)-**3b**.

Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.15; H, 5.84; N, 4.72.

(*E,Z*)-3-(2-Aminophenylthio)-3-phenylprop-2-enenitrile (*E,Z*-**3c**).

A mixture of **1** (3 mmoles) and **2c** (3 mmoles) was heated at 70° for 10 hours. The resulting oil (*E,Z*)-**3c** was identical by ir spectrum and tlc to the compound prepared according to the procedure reported in note 7. The nmr spectrum of (*E,Z*)-**3c** showed the presence of the *E,Z* vinyl thioether in a molar ratio of 38:62.

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.28; H, 4.81; N, 11.15.

Cyclization of **3** to **8** and/or **9**.

2-Phenylbenzothiazole (**8**).

A solution of (*E*)-**3b** (2 mmoles) in dimethyl sulfoxide (15 ml.) was refluxed for 14 hours. 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. Column chromatography of the residue gave **8** (25%), m.p. 115° [lit. (18) m.p. 114°] identical with an authentic sample of 2-phenylbenzothiazole.

Similarly, (*Z*)-**3b** gave **8** in 40% yield.

2-Cyano-3-phenyl-4*H*-benzo[*b*][1,4]thiazine (**9c**).

A solution of (*E,Z*)-**3c** (7.5 mmoles) in dimethyl sulfoxide (15 ml.) was refluxed for 10 hours. The solution, when cold, was poured in water and extracted with diethyl ether. The organic layer, washed with water, was dried over anhydrous sodium sulfate and evaporated. Column chromatography of the residue gave a red orange solid **9c** in 70% yield, m.p. 211° (from 2-propanol); ir: cm^{-1} 3300 (NH), 2195 (CN), 1600 (C=C); nmr (DMSO-d_6): δ 9.68 (s, 1H, NH), 7.50 (s, 5H aromatic), 7.20-6.80 (m, 4H, aromatic); ms: 250 (M^+).

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.99; H, 4.03; N, 11.20. Found: C, 72.03; H, 4.15; N, 11.05.

Compound **8** was obtained in a yield of 20% in addition to **9c** by the method described for **9c**.

2-Ethoxycarbonyl-4*H*-benzo[*b*][1,4]thiazine (**9d**).

A solution of **3d** (2.5 mmoles) in dimethyl sulfoxide (15 ml.) was refluxed for 10 hours. 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. Column chromatography of the residue gave **9d** (82%) m.p. 142° [lit. (19) m.p. 141-142°].

Conversion of **5** (R = $COOC_2H_5$, R′ = H) into **9d**.

A solution of 5 (R = $COOC_2H_5$, R′ = H) (5 mmoles) in dimethyl sulfoxide (15 ml.) was refluxed for 10 hours. 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. Column chromatography of the residue gave **9d** in 75% yield.

Desulfurization of **9c**.

A mixture of **9c** (2 mmoles), Raney-Nickel W-2 (7.8 g.) and toluene (150 ml.) was refluxed for 1 hour; the hot suspension was filtered, and the fitrate was evaporated. Tlc of the residue gave **10** as a yellow oil (32% yield), which by crystallization from 2-propanol had m.p. 138° [lit. (20) m.p. 138°].

Acknowledgment.

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