

Synthesis of Nitrobenzothiazolinethiones and Related Compounds *via* Intramolecular Displacement of Nitro Groups

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A number of dinitroanilines on reaction with sodium hydride in dimethylformamide produced the sodium salt which, on further reaction with carbon disulfide, cyclized to nitrobenzothiazolinethiones. In several cases benzothiazolinethione sulfides and benzothiazolinethione disulfides were also isolated.

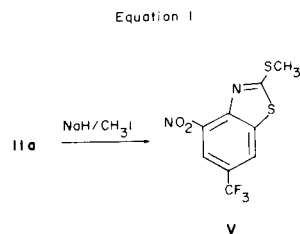
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In earlier work we have utilized the intramolecular displacement of nitro groups for the formation of the heterocyclic systems 1,3-benzodithiol-2-one (1) and 1,3-benzodithiole-2-thione (2) and the application of these reactions to the pyridine and thiophene systems has also been studied (3). We have now found that this approach can be extended to incorporate a nitrogen atom which results in the synthesis of nitrobenzothiazolinethiones.

Addition of sodium hydride to a solution of 4-amino-3,5-dinitrobenzotrifluoride (Ia) in dry dimethylformamide resulted in immediate gas evolution and the formation of a dark red solution representing the sodium salt of Ia. Addition of carbon disulfide to this reaction mixture at room temperature produced 4-nitro-6-trifluoromethyl-2-benzothiazolinethione (IIa) in 40% yield (Equation 1). Evidence that cyclization had taken place was obtained from the nmr spectrum of IIa with the aromatic hydrogens appearing as multiplets at 8.85 ppm and 8.70 ppm; the NH appears as a very broad signal at 7.5 ppm. The mass spectrum of IIa at *m/e* 280 confirms this structural assignment. Further confirmation was obtained by treatment IIa with

sodium hydride/methyl iodide which gave V, the product of methylation at sulfur and which could be unequivocally distinguished from the product of methylation at nitrogen by direct comparison (IIb, Table I) [Equation 1].

The application of this reaction sequence to other dinitroanilines and the products obtained is shown in Table I.



The structures of products shown in Table I are based on elemental analyses, nmr and mass spectral data. In all these reactions, we observed the formation of hydrogen sulfide and elemental sulfur, presumably produced by reaction of unreacted sodium hydride with carbon disulfide. Sulfides IIIb, IIIc and disulfides IVb, IVc result

Table I

Products of the Reaction of 2,6-Dinitroanilines with Sodium Hydride/Carbon Disulfide in Dimethylformamide

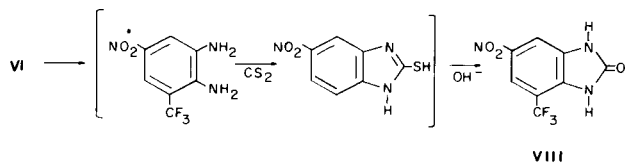
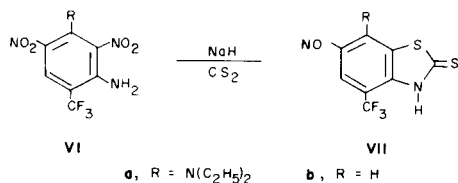
		$\xrightarrow[\text{CS}_2]{\text{NaH}}$		+		+		
	Dinitroaniline I		II		III		IV	
					Thiazolinethiones	Sulfides	Disulfides	
No	R		R'		II	III	IV	
a	H		CF ₃		40 (202-203)	-	-	
b	CH ₃		CF ₃		16 (130-133)	7 (186-188)	39 (239-241)	
c	<i>n</i> -C ₃ H ₇		CF ₃		-	-	43 (174-175)	
d	<i>i</i> -C ₃ H ₇		CF ₃		19 (104-105)	12 (211-213)	-	
e	H		CF ₃		9 (213-215)	-	-	

(a) Products were isolated by column chromatography of crude mixtures on silica gel eluting with 25% benzene in hexane (IIc), 40% benzene in hexane (IIb), 50% benzene in hexane (IIa) and chloroform (IIe, IIb, IIIc, IVb, IVc).

from further reactions of nitrobenzothiazolinethiones with sodium sulfide and sulfur present in these reaction mixtures. It is notable that these reactions involve displacements of nitro groups from nitrobenzothiazolinethiones at room temperature. Beck and Yahner (4) have described several examples of facile nitro group displacements by methanethiol anion and have observed that such displacements are activated by an alkythio functionality *ortho* to the nitro group.

The reaction of 2-amino-4-diethylamino-3,5-dinitrobenzotrifluoride (VIa) with sodium hydride and carbon disulfide produced the expected benzothiazolinethione VIIa (55%). There was no evidence for the formation of the corresponding sulfide or disulfide. Subjecting 2-amino-3,5-dinitrobenzotrifluoride (VIb) to the same reaction conditions gave rise to the benzimidazolone VIII (10%). A plausible route for the formation of VIII involves reduction of the nitro group by hydrogen sulfide or sodium hydrosulfide (5) followed by reaction with carbon disulfide and attack by hydroxide during workup (Equation 2).

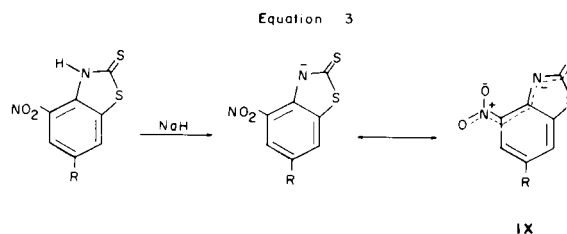
Equation 2



These results indicate that reactions involving primary amines yield nitrobenzothiazolinethiones as the only isolable products (IIa, IIe, VIIa). In contrast, the secondary amines Ib-Id produced a mixture which varied depending on the substrate; a mixture of IIb, IIIb and IVb from Ib, IVc from Ic and a mixture of IIc and IIIc from Id. This dichotomy of results is rationalized in equation 3.

The nitrobenzothiazolinethione derived from a primary amine in the presence of strong base sodium hydride yields the anion IX which is extensively delocalized over the thiazoline and nitro functionalities. The partial double bond character thus imparted to the C-N bond of the nitro group blocks nucleophilic displacement at this position by the nucleophiles sodium sulfide or sodium hydrosulfide present in these reaction mixtures. Undoubtedly the anionic character of IX also exerts electrostatic repulsion on the approaching nucleophile. This protection is not

available to nitrobenzothiazolinethiones IIb-IId which undergo varying degrees of attack by sulfur anions.



EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The nmr spectra were recorded on Varian Associates T-60 model spectrometer using TMS as an internal standard. Elemental analyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Mass spectra were carried out by Ciba-Geigy Limited, Basel, Switzerland. Silica used for chromatography was E. Merck Silica Gel 60, 70-230 mesh.

4-Nitro-6-trifluoromethyl-2-benzothiazolinethione (IIa).

To a stirred solution of 10 g (40 mmoles) of 4-amino-3,5-dinitrobenzotrifluoride (Ia) (6) in dry dimethylformamide was added 4.32 g (90 mmoles) of a 50% sodium hydride dispersion in oil in portions. This resulted in the evolution of gas and the formation of a dark red slurry. After allowing to stir at room temperature (10 minutes), 63.1 g (0.83 mole) of carbon disulfide was added dropwise at 25-30° (ice cooling). After complete addition of carbon disulfide the mixture was allowed to stir at room temperature (3 hours), poured into water (100 ml), acidified with 4*N* hydrochloric acid and extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed with water (3 × 200 ml), dried over sodium sulfate and filtered into a round bottomed flask containing silica gel (10 g). The powder obtained on distillation of chloroform in vacuum was chromatographed over silica gel (200 g) and eluted with 50% benzene in hexane. The initial fractions contained elemental sulfur and were discarded. Further elution removed an orange red band containing product. This fraction (~4 g) was distilled to dryness in vacuum and yielded 4.5 g (40%) of IIa, mp 202-203°. Recrystallization from ethanol gave analytically pure IIa, mp 202-203°; nmr (DMSO-*d*₆): δ 9.73 (m, 1H), 9.63 (m, 1H), 8.73 (broad, NH) (7); ms: *m/e* 280.

Anal. Calcd. for C₆H₃F₃O₂S₂: C, 34.28; H, 1.07; N, 10.00; S, 22.85. Found: C, 34.24; H, 1.12; S, 22.91.

Methylation of IIa to 4-Nitro-6-trifluoromethyl-2-benzothiazole Thioether (V).

To a stirred and water cooled solution of 2.8 g (10 mmoles) of IIa in dry dimethylformamide (25 ml) was added 0.5 g (10 mmoles) of 50% sodium hydride oil dispersion. After gas evolution had subsided (15 minutes), 1.7 g (12 mmoles) of methyl iodide was added dropwise which discharged the deep red color. After allowing to stir overnight, it was poured into water (150 ml) and acidified with 4*N* hydrochloric acid. The resulting mixture was extracted with chloroform (3 × 50 ml), the combined chloroform extract washed with water (3 × 500 ml), dried over sodium sulfate and solvent distilled in vacuum. The liquid residue was diluted with ethanol (10 ml) and the precipitated solids (sulfur) removed by filtration. On allowing the filtrate to stand at room temperature, thioether V crystallized from solution, yield 1.0 g (34%), mp 66-67°; nmr (acetone-*d*₆): δ 8.23 (m, 1H), 7.93 (m, 1H), 2.48 (s, 3H).

Anal. Calcd. for C₆H₃F₃N₂O₂S₂: C, 36.73; H, 1.70; N, 9.52. Found: C, 36.85; H, 1.59; N, 9.63.

3-Methyl-4-nitro-6-trifluoromethyl-2-benzothiazolinethione (IIb).

To a stirred solution of 13.24 g (50 mmoles) of 4-methylamino-3,5-dinitrobenzotrifluoride (Ib) in dry dimethylformamide (60 ml) was added

2.52 g (52.6 mmoles) of 50% sodium hydride oil dispersion followed by addition of carbon disulfide (0.36 mole) as described for IIa. After stirring (6 hours) the reaction mixture was poured into water (400 ml) and made strongly acidic with 4*N* hydrochloric acid. This mixture was extracted with chloroform (150 ml) and the insoluble solids filtered, washed with water and dried. This gave 4.0 g of disulfide IVb, mp 235-238°. Recrystallization of IVb from DMSO gave 3.2 g of product, mp 238-240°. The chloroform extract was washed with water (2 × 50 ml), dried over sodium sulfate and filtered into a flask containing silica gel (10 g). The residue obtained on distillation of chloroform to dryness was chromatographed on silica gel (200 g). Elution with 40% benzene in hexane gave a fraction (500 ml) which contained sulfur and was discarded. The following fraction (600 ml) which eluted an orange-yellow band on distillation of solvent in vacuum gave 2.3 g (16%) of IIb, mp 130-133°. Recrystallization from hot ethanol gave pure IIb, mp 134-135°. Nmr (deuteriochloroform): δ 8.03 (m, 2H); 3.90 (s, 3H).

Anal. Calcd. for $C_8H_5F_3N_2O_2S_2$: C, 36.73; H, 1.70; N, 9.52. Found: C, 36.75; H, 1.78; N, 9.48.

4,4'-Dithiobis[3-methyl-6-(trifluoromethyl)-2-benzothiazolinethione] (IVb).

Further elution with chloroform gave a fraction (1200 ml) which was distilled to dryness in vacuum. The residue obtained was heated with ethanol (60 ml) and the insoluble solid suction filtered. This gave 2.3 g of solid, mp 210-215° which was purified by dissolving in hot acetone (200 ml), concentrating to 70 ml and allowing to crystallize yielded 1.45 g of IVb, mp 239-241°. Concentration of acetone filtrate to 25 ml and allowing to crystallize yielded a further 50 mg of IVb, mp 238-240°. A total of 5.49 g (30%) of IVb was isolated; nmr (DMSO- d_6): δ 8.86 (m, 1H); 7.91 (m, 1H); 4.22 (s, 3H); 3.36 (s, 3H); ms: *m/e* 560, 280.

Anal. Calcd. for $C_{18}H_{10}F_6N_4S_4$: C, 38.57; H, 1.79; N, 5.00; S, 34.29. Found: C, 38.78; H, 1.86; N, 5.01; S, 34.35.

4,4'-Thiobis[3-methyl-6-(trifluoromethyl)-2-benzothiazolinethione] (IIIb).

The acetone filtrate from IVb was distilled to dryness and the residual viscous oil on standing for several days crystallized. Recrystallization from hot ethanol gave 0.9 g (7%) of sulfide IIIb, mp 185-188° which contained traces of IVb by tlc; nmr (acetone- d_6): δ 7.75 (m, 1H), 7.23 (m, 1H), 4.06 (s, 3H), 2.05 (s, 3H); ms: *m/e* 528, 509.

4,4'-Dithiobis[3-*n*-propyl-6-(trifluoromethyl)-2-benzothiazolinethione] (IVc).

To a stirred solution of 20.5 g (70 mmoles) of 4-*n*-propylamino-3,5-dinitrobenzotrifluoride (Ic) in dry dimethylformamide (90 ml) was added 3.7 g (77 mmoles) of 50% sodium hydride dispersion in oil followed by addition of 37.8 g (0.5 mole) of carbon disulfide as described for IIa. After allowing the mixture to stir overnight at ambient temperature, it was poured into water (500 ml), acidified with hydrochloric acid and extracted with methylene chloride (2 × 170 ml). After washing with water (3 × 500 ml) and drying over sodium sulfate the solvent was removed by distillation and the residue chromatographed over silica gel (250 g). Elution with 25% benzene in hexane (2.5 $\bar{\theta}$) removed sulfur and other impurities and this fraction was discarded. Elution with chloroform gave a fraction (500 ml) which was distilled to dryness in vacuum. The residue on recrystallization from acetone-ethanol, gave 7.3 g of disulfide IVc, mp 174-175°. Further elution with 20% ethanol in chloroform gave a fraction (400 ml) which was distilled to dryness. The residual solid on recrystallization from acetone-ethanol gave 1.83 g of IVc, mp 174-175°. This gave a total yield of 9.13 g (43%) of IVc; nmr (deuteriochloroform): δ 7.90 (d, 1H), 7.65 (d, 1H), 4.90 (m, 2H), 1.80 (m, 2H), 1.20 (t, 3H); ms: *m/e* 616, 308.

Anal. Calcd. for $C_{22}H_{18}F_3N_3O_2S_2$: C, 42.86; H, 2.92; N, 4.55. Found: C, 42.68; H, 3.00; N, 4.66.

3-*iso*Propyl-4-nitro-6-trifluoromethyl-2-benzothiazolinethione (IIc).

The reaction was carried out and worked up as described under IVc us-

ing 20.5 g (70 mmoles) of 4-*isopropylamino*-3,5-dinitrobenzotrifluoride (Id), 3.7 g (77 mmoles) of 50% sodium hydride dispersion in oil, 37.8 g (0.5 mole) of carbon disulfide and dry dimethylformamide (90 ml). The chloroform extract was distilled to dryness and the residue chromatographed on silica gel (250 g). The column was eluted with hexane until elemental sulfur had been removed (2 $\bar{\theta}$). Further elution with 25% benzene in hexane gave a fraction (2 $\bar{\theta}$) which was distilled to dryness and the residue on recrystallization from hot ethanol yielded 4.3 g (29%) of IIc, mp 104-105°; nmr (deuteriochloroform): δ 7.95 (s, 2H), 4.05 (q, 1H), 2.75 (d, 6H), J = 6 Hz.

Anal. Calcd. for $C_{11}H_8F_3N_2O_2S_2$: C, 40.99; H, 2.79; N, 8.69. Found: C, 41.24; H, 3.00; N, 8.98.

4,4'-Thiobis[3-*isopropyl*-6-trifluoromethyl-2-benzothiazolinethione] (IIIc).

Fractions obtained on further elution with chloroform (400 ml) and 20% ethanol in chloroform (350 ml) were combined and evaporated to dryness and the residue recrystallized from acetone-ethanol to give 2.4 g (12%) of sulfide IIIc, mp 209-210°; nmr (deuteriochloroform): δ 7.70 (m, 1H), 7.30 (m, 1H), 5.76 (m, 1H), 1.60 (d, 6H) J = 6 Hz; ms: *m/e* 584.

Anal. Calcd. for $C_{22}H_{18}F_3N_2S_2$: C, 42.86; H, 2.92; N, 4.55. Found: C, 42.68; H, 3.00; N, 4.66.

7-Diethylamino-6-nitro-4-trifluoromethyl-2-benzothiazolinethione (VIIa).

Reaction of 8.06 g (25 mmoles) of 2-amino-3,5-dinitro-4-diethylamino-benzotrifluoride VIa in dry dimethylformamide (30 ml) with 1.26 g (26 mmoles) of 50% sodium hydride dispersion in oil at 15-20° followed by addition of 13.9 g (0.18 mole) of carbon disulfide at 20-30° was carried out as described for IIa. After allowing to stir at ambient temperature (24 hours), the reaction mixture was worked up as described and the chloroform extract chromatographed on silica gel (200 g). Elution with 30% benzene in hexane gave a fraction (750 ml) which contained mostly sulfur and was discarded. Further elution of the orange-red band gave a fraction (1750 ml) which was distilled to dryness. The residue was recrystallized from hot hexane to give 2.7 g (33.5%) of starting material VIa, mp 87-89° (mixed mp). Elution with chloroform gave a fraction (1300 ml) which was evaporated to dryness and yielded 4.8 g (55%) of VIIa. Recrystallization from hot methanol gave 3.3 g of pure VIIa, mp 155-156°; nmr (deuteriochloroform): δ 10.3-9.5 (NH) 8.20 (s, 1H), 3.35 (q, 4H), 1.25 (t, 6H).

Anal. Calcd. for $C_{12}H_{12}F_3N_3O_2S_2$: C, 41.02; H, 3.42; N, 11.97. Found: C, 41.08; H, 3.48; N, 12.00.

6-Nitro-4-trifluoromethylbenzimidazolone (VIII).

A solution of 6.28 g (25 mmoles) of 2-amino-3,5-dinitrobenzotrifluoride (VIb) in dry dimethylformamide (30 ml) was treated with 1.26 g (26.3 mmoles) of 50% sodium hydride dispersion in oil, followed by addition of 12.6 g (0.16 mole) of carbon disulfide at 20-30°. After allowing the mixture to stir at room temperature (48 hours) it was worked up by pouring into water, acidifying with hydrochloric acid and extraction with chloroform as described for IIa. The chloroform was distilled to dryness and the residue chromatographed over silica gel (150 g) and eluted with 50% benzene in hexane. The first fraction (700 ml) contained sulfur and was discarded. The following fraction (700 ml) was combined with the first chloroform fraction (500 ml). Removal of solvents in vacuum yielded a residue that was washed with hexane and suction filtered to give 2.35 g (37%) of starting material VIb, mp 89-102° (mixed mp). Further elution with chloroform gave a fraction (800 ml) which was not further investigated (8). Elution with ethanol gave a fraction (200 ml) which was distilled to dryness in vacuum and the residue obtained was recrystallized twice by dissolving in a minimum amount of hot acetone and precipitating with hexane. There was obtained 0.6 g (9.7%) of benzimidazolone VIII, mp 232-234°; nmr (DMSO- d_6): δ 8.08 (m, 1H), 7.88 (m, 1H), 3.28 (broad NH); ms: *m/e* 247.

Anal. Calcd. for $C_8H_4F_3N_3O_2$: C, 38.87; H, 1.62; N, 17.00. Found: C, 38.68; H, 1.73; N, 16.67.

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- (6) Q. R. Soper (to Eli Lilly & Co.) U. S. 3,111,403, Nov. 19, 1963; *Chem. Abstr.*, **60**, 13184c (1964).
- (7) Owing to its poor solubility the spectrum of IIa was recorded in hot DMSO. The chemical shifts given are therefore approximate.
- (8) From its nmr spectrum in deuterioacetone [δ 8.36 (d, 1H), 8.00 (d, 1H), 4.60 (broad, NH)], we tentatively ascribe the 6-nitro-4-trifluoromethyl-2-benzothiazolinethione structure to this product.