The Chemistry of Thionitroxyl Radicals

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Acetylenes react with bisamine disulfides to give thiophenes. The decomposition of bis(*N*-benzyl-*N*-methylamine) disulfide proceeds by dissociation to a thionitroxyl radical which abstracts a benzylic hydrogen atom to give the products *N*-benzylmethylamine, *N*-methylbenzalimine, and sulfur. Morpholinothionitroxyl radical also abstracts benzylic hydrogen atoms.

Thionitroxyl radicals are formed reversibly by most bisamine disulfides.[1,2] In some cases the disulfides decompose to sulfur, amine, and imine or to thioamides, which appear to be formed from amine and sulfur and imine and sulfur. For example, at 140 °C in an evacuated sealed tube bis(dibenzylamine) disulfide decomposes to *N*-benzylthiobenzamide and dibenzylammonium hydrogen sulfide.[3]

The purpose of this research was to investigate the mechanism of decomposition of benzylic amine disulfides and the chemistry of thionitroxyl radicals.

Results and Discussion

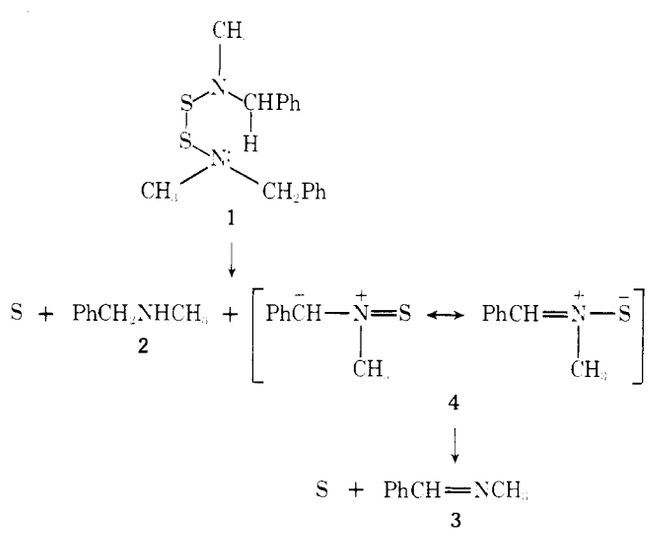
At 140 °C under nitrogen bis(*N*-benzyl-*N*-methylamine) disulfide (**1**) pyrolyzed to *N*-methylthiobenzamide. Upon attempted high vacuum distillation **1** decomposed to sulfur and a 1:1 molar ratio of *N*-benzyl-*N*-methylamine (**2**) and *N*-methylbenzalimine (**3**).

Inspection of space filling molecular models reveals that a benzylic hydrogen of one amino group lies in close proximity to the lone pair of electrons of the second amino group. Consistent with this geometry is a mechanism involving the fragmentation of **1** to a thionitrone **4** as shown in Scheme I.

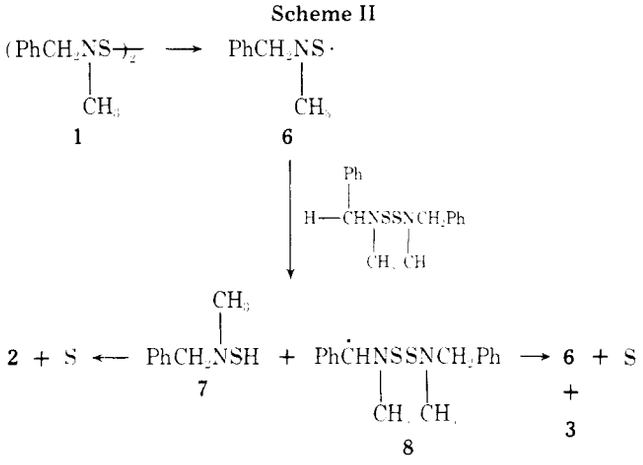
Since thionitrones might be expected to undergo 1,3 cycloaddition with acetylenes, the decomposition of the amine disulfide **1** was conducted in the presence of phenylacetylene. When run by adding acetylene to disulfide preheated to 110 °C, the reaction was violently exothermic and gave (*E*)-4,6-diphenyl-1,3-dithiafulvene (**5**) and a mixture of 2,4- and 2,5-diphenylthiophenes. The slow addition of disulfide to acetylene preheated to 140 °C was much less exothermic, and 2,4- and 2,5-diphenylthiophenes were formed in an 85:15 molar ratio and in 38% overall yield. No 1,3 cycloadduct was derived from the thionitrone **4**, and phenylacetylene was isolated by either procedure.

Bis(2,2,6,6-tetramethylpiperidine) disulfide, which lacks hydrogen atoms α to nitrogen and therefore cannot decompose to a thionitrone, also reacted with phenylacetylene to give an 82% yield of a mixture (85:15 molar ratio) of 2,4- and 2,5-diphenylthiophenes.[4]

Scheme I



Scheme II



The similarity of the diphenylthiophene isomer ratio for the reactions of **1** and the piperidine disulfide with phenylacetylene and the lack of a 1,3 cycloadduct from **4** and phenylacetylene rule out the thionitrone mechanism.

The mechanism we proposed earlier for diphenylthiophene formation upon reaction between tetramethylpiperidine disulfide and phenylacetylene involves initial dissociation of the disulfide to a thionitroxyl radical, which then adds to phenylacetylene to form an intermediate radical which collapses to a thiirene. The thiirene opens to a thioketocarbene, which undergoes cycloaddition with a second molecule of phenylacetylene to give thiophenes. The similarity of the diphenylthiophene isomer ratio for the reactions of **1** and the piperidine disulfide with phenylacetylene suggests that the decomposition of bis(*N*-benzyl-*N*-methylamine) disulfide (**1**) is initiated by dissociation of **1** to *N*-benzyl-*N*-methylthionitroxyl radical (**6**). Subsequently, **6** abstracts a benzylic hydrogen atom from a second molecule of **1** to form thiohydroxylamine **7** and benzylic radical **8**. Finally, **7** decomposes[5] to **2** and sulfur while **8** collapses to **3**, sulfur, and **6**, as shown in Scheme II.

In order to show that thionitroxyl radicals such as **6** are capable of benzylic hydrogen atom abstraction, bis(morpholine) disulfide (**9**) was separately reacted at 140 °C under nitrogen with *N*-benzyl-*N*,*N*-dimethylamine, **2**, and phenylacetonitrile.[6] Each reaction produced *N*-morpholinothiobenzamide (**10**), morpholine, and sulfur. The radical mechanism for these reactions is presented in Scheme III and is supported by the fact that molecular oxygen completely inhibits each reaction.

The formation of thiophenes upon reaction between bisamine disulfides and acetylenes appears to be fairly general.

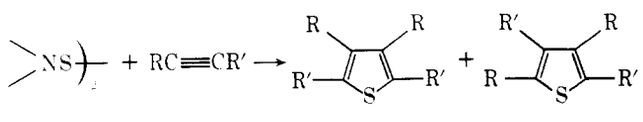


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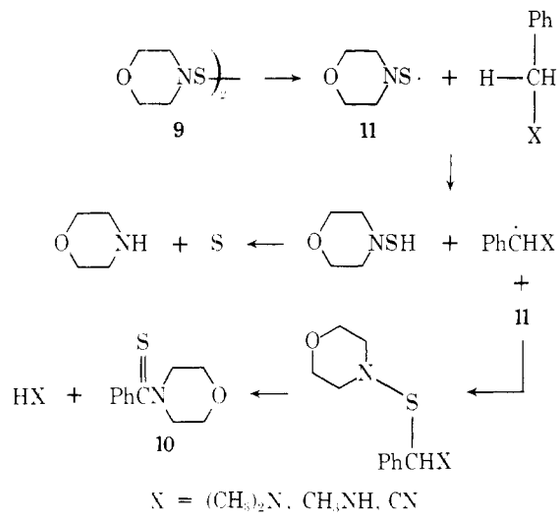
Table I

RC≡CR′ R	RC≡CR′ R′	Registry no.	Amine disulfide	Thiophene ratio 2,4	Thiophene ratio 2,5	Overall yield, %
H	Ph	536-74-3	1	85[f]	15[g]	38[a]
H	Ph		A[d]	85	15	82[a]
H	Ph		A	70	30	37[b]
H	Ph		B[d]	75	25	52[a]
H	Ph		B	85	15	37[b]
H	Ph		S_8[e]	100	0	38[b]
H	CO_2CH_3	922-67-8	B	0	100[h]	48[a]
H	CO_2CH_3		B	0	100	27[b]
Ph	$CO_2C_2H_5$	2216-94-6	B		100[c,i]	67[a]
CO_2CH_3	CO_2CH_3	762-42-5	B			38[a]
CO_2CH_3	CO_2CH_3		B			24[b]
Ph	Ph	501-65-5	A	0	0	No reaction[a]
H	$(CH_3)_3C$	917-92-0	A	0	0	S_8

[a] For 3 h at 140 °C. [b] For 24 h in refluxing chlorobenzene at 132 °C. [c] Diethyl 3,4-diphenyl-2,5-thiophenedicarboxylate. [d] A: bis(2,2,6,6-tetramethylpiperidine) disulfide; registry no., 14045-39-7. B: bis(morpholine) disulfide; registry no., 103-34-4. [e] Registry no.: S_8, 10544-50-0. [f] Registry no.: 3328-86-7. [g] Registry no.: 1445-78-9. [h] Registry no.: 4282-34-2. [i] Registry no.: 65818-64-6.

Scheme III

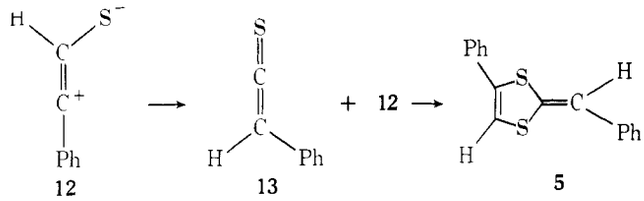


The preliminary results and the proposed thioketocarbene mechanism have been reported.[4] Here we present the experimental details and additional data as outlined in Table I. Yields are higher when the acetylene and disulfide are heated to 140 °C under nitrogen than when refluxed at 132 °C in chlorobenzene. The piperidine disulfide gives a higher overall yield of thiophene with phenylacetylene than morpholine disulfide with phenylacetylene.

Two symmetrical acetylenes give divergent results. Diphenylacetylene is unreactive, and dimethyl acetylenedicarboxylate gives tetramethyl thiophenetetracarboxylate in 38% yield. *tert*-Butylacetylene reacts with the piperidine disulfide to give sulfur but no thiophene. In this case, the intermediate thiirene or thioketocarbene decomposes to sulfur and *tert*-butylacetylene faster than it adds a second molecule of *tert*-butylacetylene to form a thiophene.

Thioketocarbenes are known to undergo 1,3-dipolar cycloaddition with carbon disulfide to form 1,3-dithiole-2-thiones.[7] The fact that we obtained 1,3-dithiole-2-thiones from reaction of carbon disulfide, acetylenes, and bisamine disulfides provides additional support for the proposed thioketocarbene mechanism. This reaction is reported in a subsequent paper.[8]

The formation of **5**, observed in the reaction between **1** and phenylacetylene discussed earlier, can now be understood as arising from the 1,3-dipolar cycloaddition between phenylthioketocarbene **12** and phenylthioketene **13**, which is produced by rearrangement[9] of **12**.



All of our results support the proposed thioketocarbene mechanism for thiophene formation from bisamine disulfides and acetylenes. However, we have conducted two experiments to eliminate the possibility that sulfur is responsible for the thiophene formation. First, morpholine and piperidine disulfides were recovered unchanged from refluxing chlorobenzene and from heating at 140 °C in a Parr bomb under nitrogen. Second, phenylacetylene reacted with sulfur in refluxing chlorobenzene to form 2,4-diphenylthiophene, exclusively.

In summary, the decomposition of **1** is initiated by dissociation to a thionitroxyl radical **6** which abstracts a benzylic hydrogen atom from **1** to form the thiohydroxylamine **7** and benzylic radical **8**, which then decompose to the observed products as shown in Scheme II.

Thionitroxyl radicals react with acetylenes to form thioketocarbenes which react with acetylenes, carbon disulfide, and phenylthioketene to form thiophenes, 1,3-dithiole-2-thiones and a dithiafulvene, respectively.

Experimental Section

All boiling points and melting points are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 237 infrared spectrophotometer. NMR spectra were recorded on a Jeol-C-60M spectrometer with Me_4Si as an internal standard. Mass spectra were taken on an Hitachi Perkin-Elmer RMU-6 spectrometer with an ionizing potential of 70 eV. Microanalyses were done by Galbraith Laboratories, Inc. The disulfide **9** was purchased from ICN Pharmaceuticals, Inc., and recrystallized from ethyl acetate before use. The amines **2** and *N*-benzyl-*N*,*N*-dimethylamine and the acetylenes phenylacetylene, ethyl phenylpropiolate, and dimethyl acetylenedicarboxylate were purchased from Aldrich Chemical Co., Inc., and methyl propiolate from Chemical Samples Co. The acetylenes diphenylacetylene[10] and *tert*-butylacetylene,[11] the disulfides[12,13] **1** and bis(2,2,6,6-tetramethylpiperidine) disulfide, and the imine[14] **3** were prepared according to the literature procedures.

Thermolysis of Bis(*N*-benzyl-*N*-methylamine) Disulfide (1). A distilling apparatus connected to a high vacuum line by all glass

fittings was charged with 15.2 g (0.05 mol) of **1** and heated to 140 °C at 1.0×10^{-4} mmHg. At this temperature 12.0 g of a colorless liquid was removed from an ice–water trap. The liquid was a mixture of imine **3** [1640 cm^{-1} (C=N)] and amine **2** [3280 cm^{-1} (N–H)]. Separation of **2** and **3** was accomplished by dissolving the liquid in Et_2O and extracting the resulting solution three times with 5% HCl. The ether layer was separated, dried ($MgSO_4$), and evaporated, giving 5.5 g (92%) of **3**: IR (neat) 3050, 2940, 2850, 1640, 1575, 1440, 1305, 1000, 900, 750, 690 cm^{-1}; mass spectrum, *m/e* (relative intensity) 119 (100), 118 (100), 103 (6), 102 (9), 91 (52), 78 (48), 77 (70), 63 (22), 51 (48), 42 (96).

The water layer was neutralized with Na_2CO_3 and extracted with Et_2O. The ether layer was separated, dried ($MgSO_4$), and evaporated, giving 6.0 g (99%) of **2**: IR (neat) 3280 cm^{-1}; mass spectrum, *m/e* (relative intensity) 121 (72), 120 (100), 119 (17), 118 (28), 92 (17), 91 (75), 78 (14), 77 (17), 44 (89), 42 (58).

The solid residue in the distilling flask was identified as sulfur in quantitative yield.

Heating 15.2 g of **1** under N_2 at atmospheric pressure at 140 °C for 1 h gave a residue from which 5.1 g of a mixture of **2** and **3** was distilled. Treatment of the pot residue with acetone gave a solid which was filtered and identified as sulfur. The acetone was evaporated to give a brown solid which was recrystallized from benzene–petroleum ether (30–60 °C) to give 2.5 g (33%) of *N*-methylthiobenzamide: mp 79 °C (lit.[15] mp 79 °C); IR (KBr) 3300, 1960, 1530, 1345, 1240, 1030, 945, 770, 690 cm^{-1}; mass spectrum, *m/e* relative intensity) 151 (88), 150 (59), 121 (100), 118 (36), 104 (15), 91 (24), 77 (94), 51 (70), 40 (76).

(*E*)-4,6-Diphenyl-1,3-dithiafulvene (5). To 15.0 g (0.05 mol) of **1** heated to 110–115 °C under N_2 was added 10.0 g (0.10 mol) of phenylacetylene dropwise. Upon completion of the addition the reaction became extremely exothermic, at which time the heat was removed. The cooled reaction mixture was treated with Et_2O, whereupon a yellow precipitate formed. Recrystallization of the solid in benzene gave 0.31 g (5%) of **5**: mp 197 °C (lit.[16] 197–198 °C; IR (KBr) 3055, 1550, 1482, 1430, 1183, 925, 895, 809, 735, 680 cm^{-1}; NMR (CCl_4) δ 6.30 (1, s), 6.37 (1, s), 7.14 (5, s), 7.25 (5, s); mass spectrum, *m/e* (relative intensity) 268 (100), 237 (12), 236 (18), 135 (11), 134 (90), 121 (45), 102 (29), 90 (49), 77 (28), 69 (20), 63 (31).

The ether was evaporated and the residue chromatographed over silica gel to give 8% of 2,4-diphenylthiophene and 32% of *N*-methylthiobenzamide.

General Procedure for Reactions between Phenylacetylene and Bisamine Disulfides. A molar ratio for phenylacetylene to bisamine disulfide was 4:1 for these experiments. To phenylacetylene maintained at 140 °C under N_2 was added bisamine disulfide over a 15-min period. The mixture was heated for 3 h, cooled, and evacuated on a high vacuum line (1×10^{-4} mmHg) for several hours to remove excess phenylacetylene. The residue was chromatographed on silica gel with petroleum ether (30–60 °C) as eluent, giving a mixture of 2,4- and 2,5-diphenylthiophenes. The thiophene mixture was separated using a GLC instrument fitted with a 6 ft SE-52 column and programmed from 100 to 300 °C at 30 °C/min with a flow rate of 30 mL/min. The retention times were 9.8 and 13.3 min for 2,4- and 2,5-diphenylthiophene, respectively. Experiments conducted by dissolving the same molar ratio of phenylacetylene to bisamine disulfide in 15 mL of chlorobenzene and refluxing for 24 h under N_2 were treated by the same procedure as above. The results are summarized in Table I.

General Procedure for Reactions between Bisamine Disulfides and Acetylenes. The acetylenes and either **9** or bis(2,2,6,6-tetramethylpiperidine) and disulfide were mixed together in a 4:1 molar ratio and heated for 3 h under N_2 at 140 °C. The reaction mixture was evacuated after cooling, and the resulting residue was chromatographed on silica gel. Experiments conducted in 15 mL of chlorobenzene were treated as mentioned in the preceding procedure.

Diethyl 3,4-Diphenyl-2,5-thiophenedicarboxylate. From 1.18 g (5.0 mmol) of **9** and 3.74 g (20.0 mmol) of ethyl phenylpropiolate, 1.27 g (67%) of the thiophene was formed: mp 141 °C (lit.[17] 141–142 °C); IR (KBr) 3075, 3000, 1730, 1700, 1450, 1375, 1310, 1230, 1100, 1010, 770, 700 cm^{-1}; NMR (CCl_4) δ 1.1 (6, H, J = 7.0 Hz), 4.1 (4, q J = 7.0 Hz), 7.0 (10, m); mass spectrum, *m/e* (relative intensity) 380 (100), 335 (41), 305 (48), 287 (62), 263 (14), 234 (31), 189 (41), 89 (28), 77 (7), 51 (10).

Dimethyl 2,5-Thiophenedicarboxylate. From 0.67 g (8.0 mmol) of methyl propiolate and 0.47 g (2.0 mmol) of **9**, 0.20 g (48%) of the thiophene was formed: mp 149 °C (lit.[18] 184–149 °C); IR (KBr) 2990, 2950, 1710, 1590, 1475, 1430, 1250, 800 cm^{-1}; NMR (CCl_4) δ 3.80 (6, s), 8.42 (2, s); mass spectrum, *m/e* (relative intensity) 200 (15), 171 (19), 169 (42), 156 (15), 140 (31), 114 (31), 112 (100), 82 (23), 43 (31).

Tetramethyl Thiophenetetracarboxylate. From 1.18 g (5.0 mmol) of **9** and 2.84 g (20.0 mmol) of dimethyl acetylenedicarboxylate, 0.61 g (39%) of the thiophene was formed: mp 125 °C (lit.[19] 125–126 °C); IR (KBr) 2999, 1710, 1540, 1460, 1250, 975 cm^{-1}; NMR (CCl_4) δ 3.90 (s); mass spectrum, *m/e* (relative intensity) 316 (29), 285 (100), 227 (10), 198 (10), 111 (36), 59 (77).

***N*-Morpholinothiobenzamide (10).** A solution of 5.4 g (40.0 mmol) of *N*-benzyl-*N*,*N*-dimethylamine and 1.18 g (5.0 mmol) of **9** was refluxed for 3 h under N_2. After cooling 10 mL of Et_2O was added, causing the precipitation of **10**. Recrystallization from Et_2O gave 0.9 g (87%): mp 137–138 °C (lit.[6] 137–138 °C); IR (KBr) 2950, 2900, 2840, 1485, 1468, 1420, 1325, 1090, 750, 690 cm^{-1}; NMR ($CDCl_3$) δ 3.52 (4, m), 3.75 (2, m), 4.32 (m, 2), 7.17 (5, s); mass spectrum, *m/e* (relative intensity) 207 (51), 206 (24), 176 (10), 174 (10), 164 (15), 130 (6), 122 (18), 121 (100, 104 (22), 91 (18), 86 (19), 77 (37), 58 (15), 51 (18).

From 1.18 g (5.0 mmol) of **9** and 1.21 g (10.00 mmol) of **2** heated for 6 h under N_2, 0.7 g (68%) of **10** was produced. From 1.18 g (5.0 mmol) of **9** and 1.17 g (10.0 mmol) of phenylacetonitrile refluxed for 6 h under N_2, 0.6 g (58%) of **10** was formed.

Registry No.—**1**, 62158-05-8; **2**, 103-67-3; **3**, 622-29-7; **5**, 40753-18-2; **6**, 65943-33-1; **10**, 2032-36-2; **11**, 65943-34-2; *N*-methylthiobenzamide, 5310-14-5; tetramethyl thiophenetetracarboxylate, 6579-15-3; *N*-benzyl-*N*,*N*-dimethylamine, 103-83-3.

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