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2-Aminothiophene. Heterocyclization of Benzylthionitriles (1,2)

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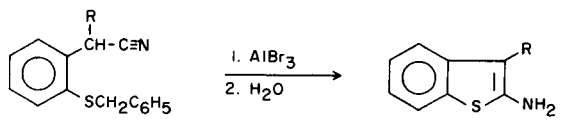
Synthesis of unstable 2-aminothiophene by way of its hydrochloride salt has been achieved in excellent yield. The key reaction in the scheme involves a novel heterocyclization of benzylthionitriles, which would appear to have general utility. Spectral and physical properties are tabulated and a possible mechanism is proposed.

Previously reported attempts to synthesize elusive 2-aminothiophene (I) have involved the obvious reduction of 2-nitrothiophene (5). In general the product was isolated as the stannous chloride double salt, which is stable and has been used in investigations of the chemistry of 2-aminothiophene (6b,c). However, the instability of the neutralized product, reported to be free 2-aminothiophene, and the very low yields involved (8-10%) would cast doubt as to the true character of the materials isolated. The absence of a practical method for preparing such a simple and interesting heterocycle as 2-aminothiophene made its synthesis an inviting area of investigation.

Previous work in this laboratory has shown that *o*-benzylthiophenylacetonitriles of the type II are readily cleaved in the presence of a Lewis acid such as aluminum bromide, to produce 2-aminobenzo[*b*]thiophenes (III) in excellent yields (Scheme I) (7). This reaction offered the intriguing possibility of obtaining 2-aminothiophene (Ia) if the appropriate benzylthionitrile (IVa) were employed.

SCHEME I



II III

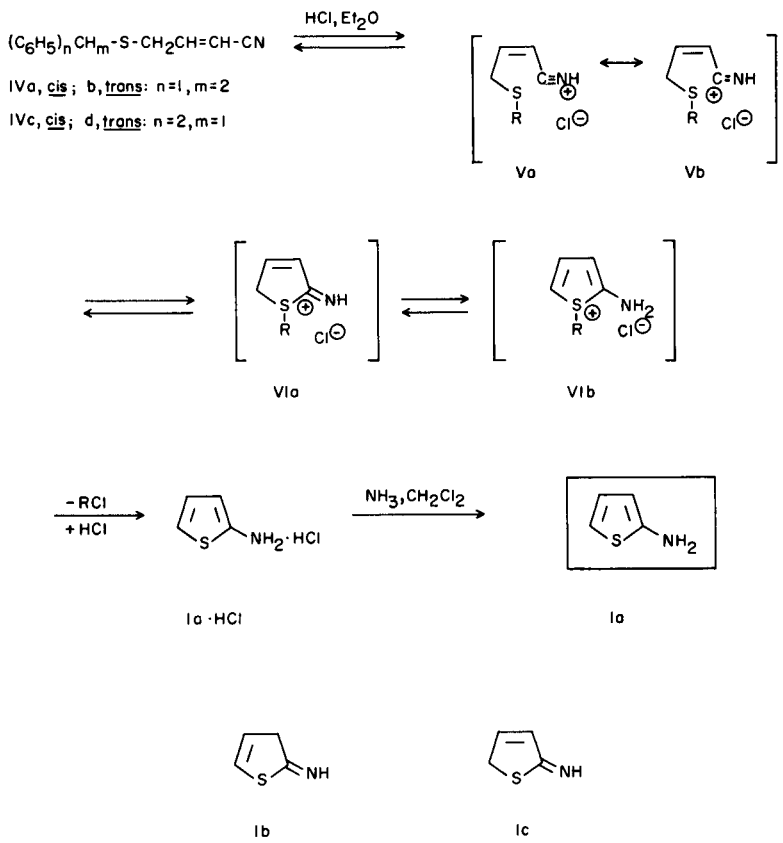
Accordingly, the prerequisite *cis*-γ-benzylthiocrotononitrile (IVa) was synthesized. However, treatment with aluminum bromide failed to yield any of the desired heterocyclization product. The complicating factor presumably was the introduction of water to cause decomposition of the intermediate complex. To avoid hydrolytic conditions, alternative Lewis acids were considered, and anhydrous hydrogen chloride seemed to be ideally suited. In this case, the intermediate complex formed after heterocyclization would simply be the stable hydrochloride salt (Ia·HCl) (6).

Indeed, when IVa was treated with anhydrous hydrogen chloride (Scheme II) in a dipolar, aprotic solvent (generally diethyl ether) a crystalline product soon began to precipitate, and in fact, Ia·HCl was at hand (54% yield).

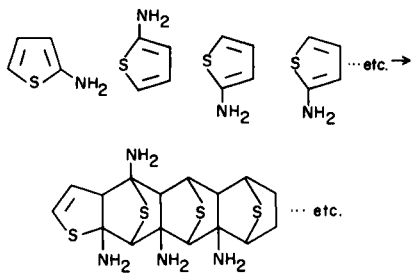
Data from the nmr spectrum are presented in Table 1. The ratio of ammonium protons to those of the thiophene ring is 3:3 which supports the amino tautomeric form Ia for the hydrochloride and rules out the alternative imino tautomers (Ib and Ic) (8). Chemically the structure was further characterized by the facile transformation to the known *N*-benzoyl (5) and *N*-acetyl (6) derivatives (9). The hydrochloride salt is very stable and can be stored for extended periods in a tightly closed bottle.

Attempts to produce the free base by neutralization of an aqueous solution of the hydrochloride resulted only in decomposition. However, it was obtained by introduction

SCHEME II



of anhydrous ammonia into a suspension of 2-aminothiophene hydrochloride (Ia·HCl) in methylene chloride. By the use of low-temperature techniques, the free base was isolated as colorless crystals (m.p. 12-13°, 51% yield). The product proved to be quite stable when maintained in an inert atmosphere below its melting point. However, either melting or exposure to air resulted in immediate decomposition producing a brown glass. Although the nature of this polymer was not investigated, it is reasonable to suggest that diene polymerization is involved with alternating or random arrangement of the amino groups.



VII

Transanular tautomerism of the polymer structure VII could give free thiol and imino groups. The imino groups would be subject to facile hydrolysis to keto groups. The resulting keto-thiol polymer could be tautomeric with a transanular hemimercaptol; reaction between the two tautomeric forms could give a cross-linked mercaptol polymer.

2-Aminothiophene (Ia) was stable enough in chloroform solution to permit determination of spectra. The nmr spectrum with an amino to thiophene-ring proton ratio of 2:3, as well as the infrared spectrum (Table I) with its characteristic amino absorption peaks, confirmed the amino structure Ia in contrast to the imino structure (Ib, Ic).

There are at least two likely mechanistic pathways for the formation of 2-aminothiophene hydrochloride (Ia·HCl) from IVa. The first (Scheme II) would involve initial protonation of the nitrile group followed by ring closure producing the sulfonium ion intermediate (VIa, b). The intermediate would then lose an equivalent of benzyl halide and add an equivalent of hydrogen chloride (not necessarily in that order) to give the product (Ia·HCl). A second possibility would simply involve cleavage of the

TABLE I

Spectral Properties and Melting Points of 2-Aminothiophene and Derivatives

Compound	δ (Amino H)	δ (Thiophene H)	cm^{-1}	M.P., °C
2-Aminothiophene (Ia)	3.78 (s, 2) (a)	6.07-6.66 (cm, 3)	3420, 3360	12-13
2-Aminothiophene·HCl (Ia·HCl)	4.68 (s, 3) (b)	7.23-7.95 (cm, 3)		130 (dec)
2-Acetamidothiophene			3290, 1640, 1580	161-161.5
2-Benzamidothiophene			3240, 1635 1560	173-174

(a) In $CDCl_3$ solvent. (b) In CF_3COOH solvent.

TABLE II

NMR Spectra for $(C_6H_5)_nCH_m$-S-CH_2CH=CHCN (IV)

Compound		Ha	Hb	Hc	Hd	He
n = 1	IVa	5.15-5.34 (d, 1) (a)	6.13-6.58 (cm, 1)	3.20-3.35 (d, 2)	3.68 (s, 2)	7.35 (s, 5)
m = 2	IVb	5.17-5.44 (d, 1)	6.28-6.83 (cm, 1)	2.90-3.04 (d, 2)	3.60 (s, 2)	7.35 (s, 5)
n = 2	IVc	4.87-5.06 (d, 1)	5.92-6.36 (q, 1)	3.12-3.25 (d, 2)	5.10 (s, 1)	7.15-7.47 (cm, 10)
m = 1	IVd	5.00-5.26 (d, 1)	6.32-6.72 (cm, 1)	2.93-3.08 (d, 2)	5.08 (s, 1)	7.20-7.56 (cm, 10)

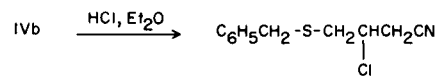
(a) Refers to splitting: s = singlet, d = doublet, q = quartet, cm = complex multiplet.

TABLE III

Analytical Data for $(C_6H_5)_nCH_m$-S-CH_2CH=CHCN (IV)

Compound		M.P. or B.P., °C	Formula	*Anal.* Calcd. %C	%H	%S	*Anal.* Found %C	%H	%S
n = 1	IVa	b.p. 125-130 (0.2 mm)	$C_{11}H_{11}NS$	69.80	5.86	16.94	69.61	6.02	17.06
m = 2	IVb	b.p. 129-133 (0.2 mm)	$C_{11}H_{11}NS$	69.80	5.86	16.94	69.91	6.03	16.78
n = 2	IVc	m.p. 45-47	$C_{17}H_{15}NS$	76.94	5.70	12.08	76.69	5.83	11.82
m = 1	IVd	m.p. 107-109	$C_{17}H_{15}NS$	76.94	5.70	12.08	76.88	5.80	12.31

carbon-sulfur bond of the benzylmercapto group followed by ring closure of the resulting thiol-nitrile. Experimentally, it was found that when *trans*-γ-benzylthiocrotononitrile (IVb) was treated in the same manner as the *cis* isomer only the addition product VIII was formed.



VIII

This fact would be consistent with Scheme II and its required *cis* stereochemistry, while if only simple cleavage of the benzyl group were involved, its removal should be observed in the present experiment with the *trans* precursor IVb. Also, consideration of the absence of subsequent ring closure of VIII suggests that some functionality requirements are operative. Apparently the absence of fixed stereochemistry (as in IVa) precludes ring closure under the conditions employed; this question will require further investigation.

The possibility that addition could be competing with heterocyclization could account for the relatively low yield of hydrochloride (Ia·HCl) from *cis*-γ-benzylthiocrotononitrile (IVa). With this in mind, the corresponding *cis*-*S*-benzhydryl derivative IVc was synthesized, and the heterocyclization reaction was carried out. The improved yield (82%) could be attributed to the greater leaving ability of the benzhydryl group (10), which would thus reduce the competing reaction.

The required thio ethers (IVa-d) were readily synthesized by the reaction of benzyl or benzhydryl mercaptan with either *cis* or *trans*-γ-bromocrotononitrile, respectively, in ether solvent; triethylamine was used to neutralize the hydrogen bromide which formed. Physical and spectral data for these compounds are compiled in Tables II and III.

The possibility of general applicability of this new heterocyclization reaction was suggested by the quantitative conversion of *o*-benzylthiophenylacetonitrile (II, R = H) and α,α-dimethyl-*o*-benzylthiophenylacetonitrile into 2-aminobenzo[*b*]thiophene hydrochloride and 2,3-dihydro-3,3-dimethyl-2-iminobenzo[*b*]thiophene hydrochloride (11), respectively (previously reported in 80 and 86% yields).

EXPERIMENTAL

All melting points are corrected while boiling points are uncorrected. NMR spectra were obtained on a Varian A-60 spectrometer using TMS as an internal standard. IR spectra were measured on a Beckman IR-8 spectrophotometer. Analyses were performed by Galbraith Microanalytical Laboratories, Nashville, Tennessee.

Preparation of γ-Benzyl- and γ-Benzhydrylthiocrotononitriles (IV).

All four compounds of this series (IVa-d) were prepared using the procedure described herewith for *cis*-γ-benzhydrylthiocrotononitrile (IVc). The physical properties and analytical data are listed in Tables II and III.

To a cooled solution of 9.5 g. (0.065 mole) of *cis*-γ-bromocrotononitrile (12) and 13.0 g. (0.065 mole) of benzhydryl mercaptan in 50 ml. of anhydrous ethyl ether was added dropwise 6.6 g. (0.065 mole) of triethylamine in 50 ml. of ether. The mixture was stirred at room temperature for 4 hours, after which 50 ml. of water was added and the ether phase was separated. The ether solution was washed with 5% hydrochloric acid (2 x 30 ml.) and with saturated sodium chloride solution (30 ml.) followed by drying over anhydrous magnesium sulfate. Removal of the ether *in vacuo* gave a quantitative yield of a yellow oil. After the oil had been dissolved in 15 ml. of ether the solution was cooled in a dry ice-acetone bath, whereupon colorless granular crystals of IV began to separate, yield 12.4 g. (71%), m.p. 45-47°; ν max (potassium bromide), 2220 cm^{-1} (m, C≡N).

2-Aminothiophene Hydrochloride (Ia·HCl).

(a) From IVc.

A solution of 11.45 g. (0.043 mole) of IVc in 100 ml. of anhydrous ether was saturated with anhydrous hydrogen chloride while cooling in an ice bath. The mixture was stirred for 5 hours at room temperature. Excess hydrogen chloride was removed under reduced pressure and filtration gave colorless plates of Ia·HCl, 4.90 g. (82%); m.p. dec. above 130°.

Anal. Calcd. for C_4H_6ClNS: C, 35.42; H, 4.46; Cl, 26.15. Found: C, 35.56; H, 4.37; Cl, 25.96.

(b) From IVa.

A solution of 10.4 g. (0.055 mole) of IVa was treated in the same manner as described in Method (a) to give 4.04 g. (54%) of pale yellow plates. The infrared spectrum was identical with that of the product (Ia·HCl) obtained from IVc.

2-Aminothiophene (Ia).

A cooled suspension of 5.00 g. (0.037 mole) of Ia·HCl in 25 ml. of methylene chloride was saturated with ammonia gas (20 minutes). The ammonium chloride was removed by filtration (nitrogen), and the methylene chloride was removed *in vacuo*. Distillation of the remaining liquid yielded 1.05 g. (29%); however, if instead, the residue was extracted with 10% methylene chloride-hexane (5 x 15 ml.), and the combined extracts were cooled in a dry ice-acetone bath, crystalline 2-aminothiophene was obtained. Filtration in a dry ice-jacketed funnel (nitrogen) gave 1.86 g. (51%) of pale yellow plates, m.p. 11-13°. An analytical sample was prepared by sublimation onto a dry ice cold finger giving colorless needles of Ia, m.p. 12-13°. Contact with air or warming above its freezing point caused rapid polymerization.

Anal. Calcd. for C_4H_5NS: C, 48.45; H, 5.08; S, 32.34. Found: C, 48.28; H, 5.29; S, 32.12.

4-Benzylthio-3-chlorobutanenitrile (VIII).

A solution of 3.78 g. (0.02 mole) of *trans*-γ-benzylthiocrotononitrile (IVb) in 40 ml. of anhydrous ether was cooled in an ice bath, then saturated with anhydrous hydrogen chloride, and stored overnight in a refrigerator. Ice water (25 ml.) was then slowly added, and the ether phase was removed. After the aqueous layer had been neutralized with sodium bicarbonate, it was extracted with ether (2 x 20 ml.). The combined ether extracts were washed

with water (2 x 20 ml.) and with saturated sodium chloride solution (1 x 20 ml.) followed by drying over anhydrous magnesium sulfate. Removal of the ether *in vacuo* left a purple liquid, which was distilled to give an analytical sample of VIII, b.p. 138-140° (0.2 mm.); n_D^{20} 1.5708; ν max (neat) 2260 cm^{-1} (w, C≡N).

Anal. Calcd. for $C_{11}H_{12}ClNS$: C, 58.52; H, 5.36; Cl, 15.71. Found: C, 58.33; H, 5.32; Cl, 15.50.

2-Acetamidothiophene.

To a mixture of 500 mg. (3.7 mmoles) of Ia·HCl and 0.2 ml. of acetic anhydride was added 0.5 ml. of pyridine. After the reaction was completed, 10 ml. of water was added, and the mixture was heated under reflux for 10 minutes and cooled giving 370 mg. (71%) of 2-acetamidothiophene as a pale yellow solid, m.p. 154-157°. Recrystallization from water (Norit) gave colorless cubets, m.p. 161-161.5° (lit. (5a) m.p. 161-162°).

2-Benzamidothiophene.

To a suspension of 500 mg. (3.7 mmoles) of Ia·HCl and 520 mg. (3.7 mmoles) of benzoyl chloride in 15 ml. of chloroform was added 2 ml. of pyridine. The mixture was stirred for 15 minutes, after which the chloroform phase was extracted with 10% hydrochloric acid (2 x 10 ml.), with water (1 x 10 ml.) and with saturated sodium bicarbonate solution (2 x 10 ml.). The combined extracts were dried over anhydrous calcium chloride. Removal of the chloroform left a purple solid which was recrystallized from dilute ethanol (Norit) to give 0.68 g. (85%) of 2-benzamidothiophene as colorless needles, m.p. 173-174° (lit. (6) m.p. 172-173°).

2-Aminobenzo[*b*]thiophene Hydrochloride.

A solution of 4.00 g. (0.016 mole) of *o*-benzylthiophenylacetonitrile (7) in 50 ml. of ether was cooled to dry ice temperature and then saturated with anhydrous hydrogen chloride (0.5 hour). The mixture was allowed to slowly warm to room temperature. Excess hydrogen chloride was removed under reduced pressure and then the mixture was filtered to give 2.72 g. (quantitative) of pale pink crystals. The infrared spectrum was identical with that prepared in 80% yield by Stacy *et al.* (7).

2,3-Dihydro-3,3-dimethyl-2-iminobenzo[*b*]thiophene Hydrochloride.

A solution of 1.00 g. (3.8 mmoles) of α,α-dimethyl-*o*-benzylthiophenylacetonitrile (11) in 25 ml. of anhydrous benzene was saturated with anhydrous hydrogen chloride (1 hour). The crystalline precipitate was filtered to give 0.84 g. (quantitative) of colorless crystals whose infrared and nmr spectra were identical with those of a sample prepared previously in 86% yield by Stacy and Wollner (11).

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(3) Dow Research Assistant, Summer 1966; NSF Summer Fellow, 1967.

(4) To whom inquiries regarding this paper should be addressed.

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