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Studies on Heterocyclic Enaminonitriles. II.[1] Synthesis and Aromatization of 2-Amino-3-cyano-4,5-dihydrothiophenes

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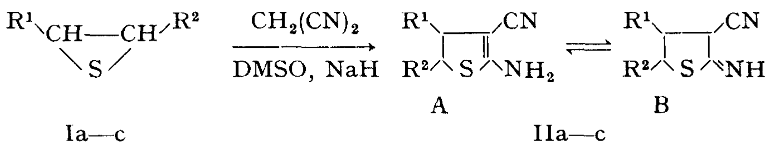
Thirane reacted with malononitrile and sodium hydride to give 2-amino-3-cyano-4,5-dihydrothiophene (IIa) in 57% yield. Similarly, 2-methyl(or 2-phenyl)thirane reacted with malononitrile to form 2-amino-3-cyano-5-methyl(or 4-phenyl)-4,5-dihydrothiophene (IIb or IIc). The reactions of the 2-benzamido(or 2-acetamido) derivatives of (IIa or c) with *N*-bromosuccinimide (NBS) in the presence of 2,2′-azobisisobutyronitrile gave the corresponding 5-bromothiophenes. On the other hand, the 2-benzamido(or 2-acetamido) derivative of IIb reacted with NBS to yield 2-benzamido(or 2-acetamido)-3-cyano-5-methylthiophene.

Keywords——thiranes; malononitrile; 2-amino-3-cyano-4,5-dihydrothiophenes; NBS; aromatization; bromination; 2-benzamido(or 2-acetamido)-3-cyanothiophenes

In the preceding paper,[1] we showed that malononitrile reacts with 1-ethoxycarbonylaziridines in the presence of sodium hydride to form 2-amino-3-cyano-1-ethoxycarbonyl-4,5-dihydropyrroles. We now describe the reactions of thiranes with malononitrile.

Snyder *et al.*[2] reported that the reaction of thirane with ethyl cyanoacetate in the presence of sodium ethoxide gives 2-amino-3-ethoxycarbonyl-4,5-dihydrothiophene in 23% yield. Under the same conditions, however, the reaction of thirane (Ia) with malononitrile gave the desired 2-amino-3-cyano-4,5-dihydrothiophene (IIa) in a very low yield together with large amounts of resinous substances. On the other hand, Campaigne *et al.*[3] reported that 2-phenyloxirane reacts with malononitrile in the presence of sodium hydride in dimethyl sulfoxide (DMSO) to produce 2-amino-3-cyano-5-phenyl-4,5-dihydrofuran in 55% yield. Therefore, we also investigated these conditions for a synthesis of 2-amino-3-cyano-4,5-dihydrothiophenes.

When a mixture of thirane (Ia), malononitrile (2.2 eq) and sodium hydride (1.2 eq) in DMSO was heated at 60°C for 3 h, 2-amino-3-cyano-4,5-dihydrothiophene (IIa) was obtained in 57% yield. Similarly, the reactions of 2-methylthirane (Ib) and 2-phenylthirane (Ic) with malononitrile gave 2-amino-3-cyano-5-methyl-4,5-dihydrothiophene (IIb) and 2-amino-3-cyano-4-phenyl-4,5-dihydrothiophene (IIc) in 62 and 50% yields, respectively. When IIa—c were treated with benzoyl chloride in pyridine, the corresponding 2-benzamido-3-cyano-4,5-dihydrothiophenes (IIIa—c) were obtained. On acetylation with acetic anhydride, IIa—c gave the corresponding 2-acetamido derivatives (IVa—c.) Some properties of II, III and IV are shown in Table I, and the spectral data are listed in Table II.

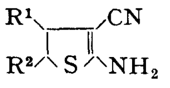


Ia—c IIa—c

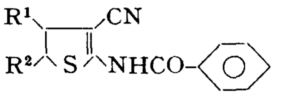
a: $R^1=R^2=H$ b: $R^1=H, R^2=CH_3$ c: $R^1=C_6H_5, R^2=H$

The infrared (IR) spectra of IIa—c exhibited a characteristic conjugated nitrile band at near 2170 cm^{-1}, and the bands due to a primary amino group at near 3400, 3310 and 3210 cm^{-1}.

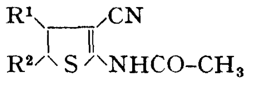
Table I. Some Properties of II, III and IV



IIa—c



IIIa—c



IVa—c

a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=C_6H_5$, $R^2=H$

Compd. No.	mp (°C) (Recrystn. solvent)	Appearance (Colorless)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
IIa	145—146 (Ether)	Prisms	57	$C_5H_6N_2S$	47.62 (47.81	4.80 4.96	22.22 22.24)
IIb	112—113 (Ether)	Prisms	62	$C_6H_8N_2S$	51.42 (51.47	5.75 5.71	19.99 19.82)
IIc	145 (Ether)	Prisms	50	$C_{11}H_{10}N_2S$	65.33 (65.81	4.98 5.02	13.86 13.56)
IIIa	132—133 (Acetone)	Prisms	79	$C_{12}H_{10}N_2OS$	62.60 (62.70	4.38 4.35	12.17 12.21)
IIIb	134—135 (Acetone)	Columns	92	$C_{13}H_{12}N_2OS$	63.92 (64.01	4.95 4.94	11.47 11.41)
IIIc	158—160 (Acetone)	Prisms	83	$C_{18}H_{14}N_2OS$	70.58 (70.27	4.61 4.57	9.15 8.76)
IVa	183—185 (Acetone)	Prisms	86	$C_7H_8N_2OS$	50.00 (49.98	4.80 4.69	16.66 16.43)
IVb	149—150 (Acetone)	Columns	83	$C_8H_{10}N_2OS$	52.74 (52.68	5.53 5.46	15.38 15.45)
IVc	180—182 (Acetone)	Columns	86	$C_{13}H_{12}N_2OS$	63.92 (63.88	4.95 4.84	11.47 11.51)

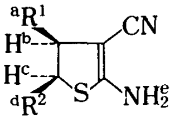
The proton magnetic resonance (PMR) spectra showed a broad singlet at near δ 4.7 (2H) indicative of primary amino protons. These observations are consistent with the enamine structures (A) rather than the imine structures (B).

In order to confirm the structures of IIa—c, we aromatized compounds III and IV by the use of *N*-bromosuccinimide (NBS).[1,4,5] When a solution of 2-benzamido-3-cyano-4-phenyl-4,5-dihydrothiophene (IIIc), NBS (1.1 eq) and 2,2′-azobisisobutyronitrile (AIBN) in carbon tetrachloride was refluxed for 1 h, 2-benzamido-5-bromo-3-cyano-4-phenylthiophene (Vc) was obtained in 29% yield together with unchanged IIIc (34%). When 2.2 eq of NBS were used, the yield of Vc increased to 84%. 2-Benzamido-3-cyano-4-phenylthiophene (VI) prepared from 2-amino-3-cyano-4-phenylthiophene[6] reacted with NBS to give Vc in 94% yield.

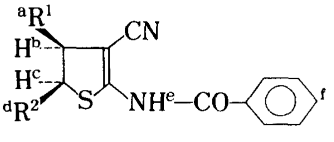
These findings suggest that IIIc was initially aromatized to VI, which then underwent bromination by NBS to form Vc. In a similar manner, the reaction of IVc and NBS (2.2 eq) gave 2-acetamido-5-bromo-3-cyano-4-phenylthiophene (VIIc), which was identical with an authentic sample prepared from 2-acetamido-3-cyano-4-phenylthiophene (VIII) and NBS.

Subsequently, the reaction of IIIb and NBS (1.3 eq) gave 2-benzamido-3-cyano-5-methylthiophene (Vb) in 44% yield, no bromo derivative being isolated. When a solution of Vb and NBS in carbon tetrachloride was refluxed, only Vb was recovered unchanged. Although Vb had the molecular composition $C_{13}H_{10}N_2OS$, which is the same as that of 2-benzamido-3-cyano-4-methylthiophene (IX) prepared from 2-amino-3-cyano-4-methylthiophene,[6] Vb was obviously not identical with the latter compound. In the PMR spectra of Vb and IX, the aromatic at C-4 in Vb appeared at higher magnetic field than the proton signal at C-5 in IX (δ 6.90 and δ 6.96 for Vb and IX, respectively). On the other hand, the methyl protons at C-5 in Vb absorbed at lower field than the methyl protons at C-4 in IX (δ 2.38 and δ 2.28 for Vb and IX, respectively). On the basis of these spectral data, Vb was assigned as 2-

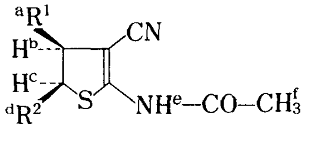
Table II. Some Spectral Data for II, III and IV



II a−c



III a−c

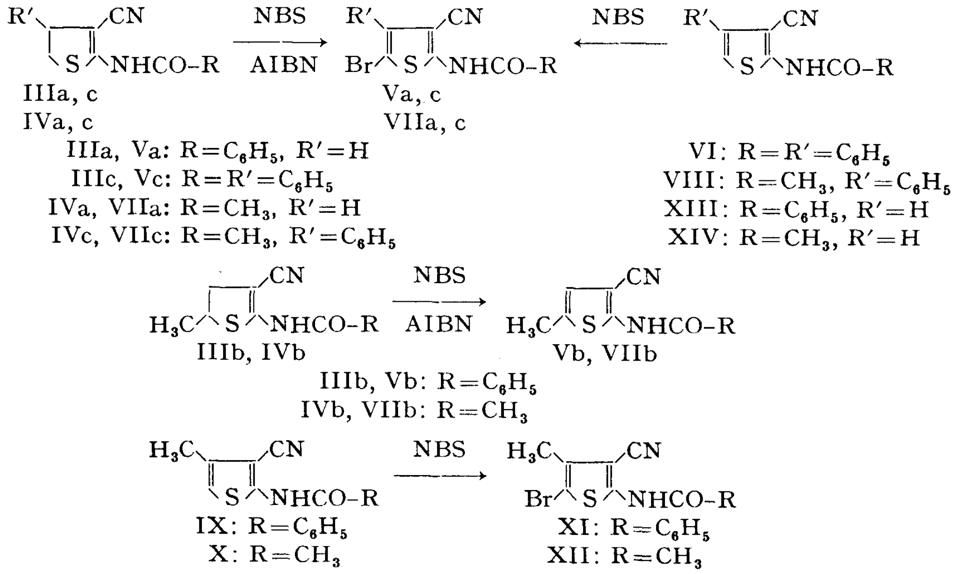


IV a−c

a: $R^1=R^2=H$
b: $R^1=H, R^2=CH_3$
c: $R^1=C_6H_5, R^2=H$

Compd. No.	IR ν_{max}^{KBr} cm^{-1} NH	CN	CO	^{1}H-NMR spectra (ppm) in $CDCl_3$ solution (J in Hz) H^a	H^b	H^c	H^d	H^e	H^f	MS m/z (M^+)
IIa	3400 3320 3215	2160	—	2.76—2.98 (m)		3.10—3.32 (m)		4.70 (br s)	—	126
IIb	3400 3310 3215	2165	—	2.99 (dd)	2.50 (dd)	3.60—3.96 (m)	1.37 (d)	4.68 (br s)	—	140
				($J_{a,b}=13$, $J_{a,c}=8$, $J_{b,c}=6$, $J_{c,d}=6$)						
IIc	3430 3305 3200	2170	—	7.15 (s)	4.28 (dd)	3.10 (dd)	3.55 (dd)	4.75 (br s)	—	202
				($J_{b,c}=7$, $J_{b,d}=8$, $J_{c,d}=11$)						
IIIa	3230	2190	1683	2.65—3.00 (m)		3.10—3.45 (m)		8.62 (br s)	7.25—7.58 (3H, m) 7.58—7.88 (2H, m)	230
IIIb	3290	2195	1692	2.97 (dd)	2.44 (dd)	3.46—3.90 (m)	1.40 (d)	8.27 (br s)	7.15—7.37 (3H, m) 7.42—7.65 (2H, m)	244
				($J_{a,b}=14$, $J_{a,c}=8$, $J_{b,c}=6$, $J_{c,d}=6.5$)						
IIIc	3320	2200	1685	7.36 (s)	4.36 (dd)	3.26 (dd)	3.82 (dd)	8.77 (br s)	7.20—7.72 (3H, m) 7.80—8.00 (2H, m)	306
				($J_{b,c}=7$, $J_{b,d}=9$, $J_{c,d}=11$)						
IVa	3240	2190	1705	2.74—3.00 (m)		3.14—3.40 (m)		9.03 (br s)	2.17 (s)	168
IVb	3230	2200	1705	3.02 (dd)	2.50 (dd)	3.64—3.96 (m)	1.40 (d)	8.89 (br s)	2.17 (s)	182
				($J_{a,b}=14$, $J_{a,c}=8$, $J_{b,c}=6$, $J_{c,d}=6.5$)						
IVc	3235	2200	1711	7.40 (s)	4.32 (dd)	3.20 (dd)	3.65 (dd)	9.08 (br s)	2.08 (s)	244
				($J_{b,c}=7$, $J_{b,d}=9$, $J_{c,d}=11$)						

Abbreviations: br s, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; s, singlet.



IIIa, Va: $R=C_6H_5$, $R'=H$
IIIc, Vc: $R=R'=C_6H_5$
IVa, VIIa: $R=CH_3$, $R'=H$
IVc, VIIc: $R=CH_3$, $R'=C_6H_5$

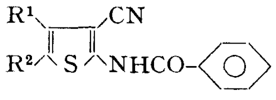
VI: $R=R'=C_6H_5$
VIII: $R=CH_3$, $R'=C_6H_5$
XIII: $R=C_6H_5$, $R'=H$
XIV: $R=CH_3$, $R'=H$

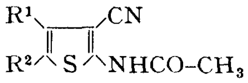
IIIb, Vb: $R=C_6H_5$
IVb, VIIb: $R=CH_3$

Chart

benzamido-3-cyano-5-methylthiophene. In contrast with Vb, the reactions of IX and 2-acetamido-3-cyano-4-methylthiophene (X) with NBS gave the corresponding 5-bromo derivatives (XI and XII) (see "Experimental"). Similarly, the reaction of IVb with NBS afforded 2-acetamido-3-cyano-5-methylthiophene (VIIb) in 43% yield.

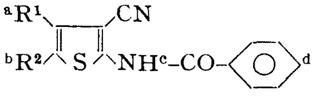
Table III. Some Properties of V and VII

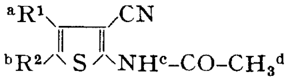

Va—c


VIIa—c

Compd. No.	R^1	R^2	Yield (%)	mp (°C) (Recrystn. solvent)	Appearance (Colorless)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
Va	H	Br	66	166—168 (CH_2Cl_2–petr. benzin)	Needles	$C_{12}H_7BrN_2OS$	46.93 (46.96	2.29 2.33	9.12 9.09)
Vb	H	CH_3	44	179—180 (Acetone–petr. benzin)	Needles	$C_{13}H_{10}N_2OS$	64.46 (63.96	4.16 4.17	11.57 11.57)
Vc	C_6H_5	Br	84	203—204 (Acetone)	Needles	$C_{18}H_{11}BrN_2OS$	56.41 (56.64	2.89 2.91	7.31 7.34)
VIIa	H	Br	56	194—195 (MeOH)	Columns	$C_7H_5BrN_2OS$	34.32 (34.61	2.07 2.05	11.34 11.54)
VIIb	H	CH_3	43	204 (Acetone–petr. benzin)	Scales	$C_8H_8N_2OS$	53.33 (53.08	4.48 4.33	15.55 15.50)
VIIc	C_6H_5	Br	56	238—239 (MeOH)	Columns	$C_{13}H_9BrN_2OS$	48.62 (48.15	2.83 2.65	8.72 8.32)

Table IV. Some Spectral Data for V and VII


Va—c


VIIa—c

Compd. No.	R^1	R^2	IR ν_{max}^{KBr} cm^{-1}			^{1}H-NMR spectra ppm (J in Hz)				MS m/z (M^+)
			NH	CN	CO	H^a	H^b	H^c	H^d	
Va	H	Br	3280	2230	1665	$^{a)}$6.99 (s)	—	9.15 (br s)	7.42—7.70 (3H, m) 7.84—8.00 (2H, m)	306, 308
Vb	H	CH_3	3255	2227	1677	$^{b)}$6.90 (s)	2.38 (s)	11.60 (br s)	7.50—7.70 (3H, m) 7.86—8.08 (2H, m)	242
Vc	C_6H_5	Br	3350	2220	1683	$^{b)}$7.67 (s)	—	12.60 (br s)	7.60—7.80 (3H, m) 8.02—8.23 (2H, m)	382, 384
VIIa	H	Br	3260	2230	1692	$^{a)}$6.92 (s)	—	9.54 (br s)	2.31 (s)	244, 246
VIIb	H	CH_3	3280	2225	1695	$^{b)}$6.83 (s)	2.33 (s)	11.50 (br s)	2.18 (s)	180
VIIc	C_6H_5	Br	3267	2220	1695	$^{b)}$7.56 (s)	—	12.14 (br s)	2.27 (s)	320, 322
XIII[7)]	H	H	3260	2225	1680	$^{a)}$6.90 (d) ($J_{a,b}=6$)	7.01 (d)	9.16 (br s)	7.40—7.67 (3H, m) 7.84—8.06 (2H, m)	
XIV[7)]	H	H	3270	2210	1688	$^{a)}$6.82 (d) ($J_{a,b}=6$)	6.95 (d)	9.15 (br s)	2.31 (s)	

Abbreviations: br s, broad singlet; d, doublet; m, multiplet; s, singlet.
a) In $CDCl_3$. *b*) In $(CD_3)_2SO$.

Finally, the reaction of IIIa with NBS resulted in the formation of 2-benzamido-5-bromo-3-cyanothiophene (Va) in 84% yield. On treatment with NBS, 2-benzamido-3-cyanothiophene (XIII)⁷⁾ was converted to Va in 84% yield. The structure of Va was supported by the analytical and spectral data. In particular, its PMR spectrum showed a one-proton singlet at δ 6.99 assigned to the proton at C-4. This absorption is at lower field than that of the C_4-proton (δ 6.90) of XIII, and at higher field than that of the C_5-proton (δ 7.01) of XIII. These observations are consistent with the assigned structure. In a similar fashion, IVa reacted with NBS to give 2-acetamido-5-bromo-3-cyanothiophene (VIIa), which was identical with an authentic specimen prepared by bromination of 2-acetamido-3-cyanothiophene (XIV).⁷⁾ Some properties of V and VII are shown in Table III and the spectral data are listed in Table IV.

On the basis of these results, it appeared that the malononitrile anion attacked at C-3 of Ib, whereas the anion attacked at C-2 of Ic. Similarly, we reported¹⁾ that the malononitrile anion attacks at C-3 of 1-ethoxycarbonyl-2-methylaziridine, while the anion attacks at C-2 of 1-ethoxycarbonyl-2-phenylaziridine. In contrast with these reactions, Campaigne *et al.*³⁾ reported that the malononitrile anion attacks at C-3 of 2-phenyloxirane to give 2-amino-3-cyano-5-phenyl-4,5-dihydrofuran.

Experimental

DMSO was distilled under reduced pressure and stored over molecular sieve 4A. All melting points are uncorrected. IR spectra were recorded on an IRA-2 spectrophotometer. PMR spectra were taken on a Hitachi R-22 spectrometer at 90 MHz or a JNM-MH-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL model JMS-01SG spectrometer.

Reaction of Malononitrile with Ia—c. General Procedure for the Preparation of IIa—c——Malononitrile (0.2 mol) was added dropwise to a stirred suspension of 50% NaH (0.12 mol) in DMSO (70 ml). The stirring was continued until evolution of gas ceased. A solution of Ia, b or c (0.1 mol) in DMSO (30 ml) was then added dropwise over a period of 0.5—1 h with stirring and ice cooling. The mixture was stirred at room temperature for 1 h, and then heated for 60°C for 3 h. After removal of the DMSO *in vacuo*, the residue was poured into ice water. The precipitate was collected, washed with ice water, dried, and recrystallized from ether.

Benzoylation of IIa—c——A solution of IIa, b or c (10 mmol) and benzoyl chloride (11 mmol) in pyridine (10 ml) was heated at 40—50°C for 1 h. The reaction mixture was poured into ice water, and the deposited crystals were collected, washed with water, dried and recrystallized from acetone.

Acetylation of IIa—c——A solution of IIa, b or c (10 mmol) in Ac_2O (10 ml) was heated at 80°C for 1 h. After the Ac_2O had been evaporated off on a water bath under reduced pressure, the residue was poured into ice water. The precipitate was collected, washed with water, dried, and recrystallized from acetone.

Reaction of IIIc with NBS——i) A solution of IIIc (5 mmol) and AIBN (50 mg) in $CHCl_3$ (15 ml) was added dropwise to a refluxed solution of NBS (5.5 mmol) and AIBN (100 mg) in CCl_4 (150 ml) over a period of 10 min, and the whole was refluxed for 1 h. The solvent was removed *in vacuo*, and the residue was basified with aq. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel with $CHCl_3$ as the eluent. The first fraction eluted with $CHCl_3$ was 2-benzamido-5-bromo-3-cyano-4-phenylthiophene (Vc) (560 mg, 29%), which was identical with an authentic sample prepared from 2-benzamido-3-cyano-4-phenylthiophene by the method described later in this paper. The second product to appear was IIIc (520 mg, 34%).

ii) A solution of IIIc (5 mmol) and AIBN (50 mg) in $CHCl_3$ (15 ml) was added to a refluxed suspension of NBS (11 mmol) and AIBN (100 mg) in CCl_4 (150 ml) over a period of 10 min, and the reaction mixture was refluxed for another 2 h. After the solvent had been removed *in vacuo*, the residue was made alkaline with aq. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give Vc (1.6 g, 84%).

Reactions of IIIa or b and IVa, b or c with NBS——A solution of IIIa or b or IVa, b or c (5 mmol) and AIBN (50 mg) in $CHCl_3$ (15 ml) was added dropwise to a refluxed suspension of AIBN (100 mg) and NBS [11 mmol in the case of IIIa or IVa or c, or 6.5 mmol in the case of IIIb or IVb] in CCl_4 (150 ml) over a period of 10 min. After removal of the solvent *in vacuo*, the residue was basified with aq. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give the thiophene derivative (Va or b, or VIIa—c), which was recrystallized from an appropriate solvent (Table III).

2-Benzamido-3-cyano-4-phenylthiophene (VI)——Benzoyl chloride (0.055 mol) was added dropwise to a solution of 2-amino-3-cyano-4-phenylthiophene⁶⁾ (0.05 mol) in pyridine (50 ml) with stirring and ice cooling, and the whole was heated at 40—50°C for 1 h. The reactants were poured into ice water, and the deposited crystals were collected, washed with water, and dried. Recrystallization from MeOH gave VI (11.55 g, 76%) as colorless prisms, mp 197°C. *Anal.* Calcd for $C_{18}H_{12}N_2OS$: C, 71.04; H, 3.98; N, 9.21. Found: C, 70.84; H, 3.99; N, 9.08. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3280 (>NH), 2200 (CN), 1670 (>CO).

2-Acetamido-3-cyano-4-phenylthiophene (VIII)——A solution of 2-amino-3-cyano-4-phenylthiophene (10 mmol) in Ac_2O (20 ml) was heated at 80°C for 1 h. After work-up as described for the acetylation of II, VIII (1.74 g, 72%) was obtained, mp 211°C (from acetone–petr. ether), colorless needles, *Anal.* Calcd for $C_{13}H_{10}N_2OS$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.18; H, 4.11; N, 11.59. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3275 (>NH), 2220 (CN), 1690 (>CO).

2-Benzamido-3-cyano-4-methylthiophene (IX)——A solution of 2-amino-3-cyano-4-methylthiophene[6] (0.05 mol) and benzoyl chloride (0.055 mol) in pyridine (50 ml) was heated at 40—50°C for 1 h. After work-up as described for the preparation of VI, IX was obtained. Recrystallization from acetone gave IX (7.93 g, 66%) as colorless prisms, mp 199—202°C. *Anal.* Calcd for $C_{13}H_{10}N_2OS$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.42; H, 4.11; N, 11.56. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3260 (>NH), 2224 (CN), 1670 (>CO). PMR (in DMSO-d_6) δ: 2.28 (3H, s, –C$\underline{H}_3$), 6.96 (1H, s, C_5–H), 7.48—7.76 (3H, m, aromatic H), 7.96—8.12 (2H, m, aromatic H), 11.78 (1H, br s, >NH).

2-Acetamido-3-cyano-4-methylthiophene (X)——A solution of 2-amino-3-cyano-4-methylthiophene (0.05 mol) in Ac_2O (50 ml) was heated at 80°C for 1 h. After work-up as described for the preparation of IV, X was obtained. Recrystallization from acetone gave X (5.27 g, 64%) as colorless prisms, mp 179—182°C. *Anal.* Calcd for $C_8H_8N_2OS$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.21; H, 4.38; N, 15.50. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3275 (>NH), 2225 (CN), 1697 (>CO). PMR (in DMSO-d_6) δ: 2.22 (3H, s, C_4–C$\underline{H}_3$ or CO–C$\underline{H}_3$), 2.24 (3H, s, CO–C$\underline{H}_3$ or C_4–C$\underline{H}_3$), 6.48 (1H, s, C_5–H), 11.66 (1H, br s, >NH).

Reaction of VI with NBS——A solution of VI (1 g) and NBS (650 mg) in CCl_4 (100 ml) was refluxed for 2 h. After removal of the solvent *in vacuo*, the residue was basified with aq. $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give Vc (1.20 g, 94%).

Reaction of VIII with NBS——A solution of VIII (800 mg) and NBS (650 mg) in a mixed solvent of CCl_4 (100 ml) and $CHCl_3$ (30 ml) was refluxed for 2 h. Work-up of the reaction mixture as described above yielded VIIc (740 mg, 69%).

Reactions of IX and X with NBS——A solution of IX or X (10 mmol) and NBS (11 mmol) in CCl_4 (200 ml) was refluxed for 2 h. Work-up of the reaction mixture as described above gave XI (3.01 g, 94%) or XII (2.31 g, 90%). 2-Benzamido-5-bromo-3-cyano-4-methylthiophene (XI) was recrystallized from MeOH to give colorless needles, mp 230—232°C. *Anal.* Calcd for $C_{13}H_9BrN_2OS$: C, 48.62; H, 2.83; N, 8.72. Found: C, 48.52; H, 2.74; N, 8.69. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3270 (>NH), 2227 (CN), 1678 (>CO). PMR (in DMSO-d_6) δ: 2.20 (3H, s, C_4–C$\underline{H}_3$), 7.44—7.70 (3H, m, aromatic H), 7.88—8.05 (2H, m, aromatic H), 12.20 (1H, br s, >NH).

2-Acetamido-5-bromo-3-cyano-4-methylthiophene (XII) was recrystallized from MeOH to give colorless needles, mp 225°C. *Anal.* Calcd for $C_8H_7BrN_2OS$: C, 37.09; H, 2.72; N, 10.81. Found: C, 37.06; H, 2.70; N, 10.76. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3270 (>NH), 2220 (CN), 1693 (>CO). PMR (in DMSO-d_6) δ: 2.17 (3H, s, CO–C$\underline{H}_3$ or C_4–C$\underline{H}_3$), 2.23 (3H, s, C_4–C$\underline{H}_3$ or CO–C$\underline{H}_3$), 12.25 (1H, br s, >NH).

Reactions of XIII and XIV with NBS——Compound XIII or XIV (5 mmol) was treated with a solution of NBS (5.5 mmol) in CCl_4 (150 ml) in the case of XIII or in a mixed solvent of CCl_4 (70 ml) and $CHCl_3$ (70 ml) in the case of XIV by the procedure described above. Purification was carried out by column chromatography on silica gel with $CHCl_3$ as the eluent. Va and VIIa were obtained in 84 and 80% yields, respectively.

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