Reactions of Halothiophenes with Acetone Enolate and Amide Ions[1]

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Acetone enolate ion undergoes photostimulated reaction with 2-chloro-, 2-bromo- and 3-bromothiophenes in liquid ammonia, affording mono- and di-thienylacetones in fair to good yields. 3-Bromothiophene reacts with the same enolate ion under stimulation by solvated electrons to form mono- and di(3-thienyl)acetones in lower yield accompanied by the corresponding secondary alcohols, except that in the presence of excess KNH_2 only debromination to thiophene occurs. Solvated electron-stimulated reactions of 2-chloro- and 2-bromothiophenes with acetone enolate ion give mainly thiophene and little thienylation. Under N_2, 3-bromothiophene and KNH_2 give 3-amino-thiophene in high yield, but not much reaction occurs under an atmosphere of air. These reactions are believed to occur by the $S_{RN}1$ mechanism. They suggest that substitutions by the $S_{RN}1$ mechanism may be generally useful in the thiophene series, especially for the preparation of 3-substituted thiophenes.

In recent years it has been discovered that simple halobenzenes react with a variety of nucleophiles under mild conditions, often under stimulation by electrons or photons, to give products of nucleophilic substitution. Nucleophiles involved in such reactions include the amide ion,[2] ketone enolate ions,[3-7] α-cyanoalkyl anions,[8] picolyl anions,[9] thiophenoxide ion,[10] and dialkyl phosphite ions.[11] Reactions of similar type, though differing in some respects, have also been observed for halonaphthalenes,[12] for 2-chloroquinoline,[13-15] and for 4-bromoisoquinoline.[16]

These reactions are believed to occur by the $S_{RN}1$ mechanism,[2] a radical chain mechanism the propagation cycle of which is represented in Scheme I, in which ArX is an aryl or heteroaryl halide and Y^- an anionic nucleophile.

Scheme I

$$[ArX]\cdot^- \longrightarrow Ar\cdot + X^-$$

$$Ar\cdot + Y^- \longrightarrow [ArY]\cdot^-$$

$$[ArY]\cdot^- + ArX \longrightarrow ArY + [ArX]\cdot^-$$
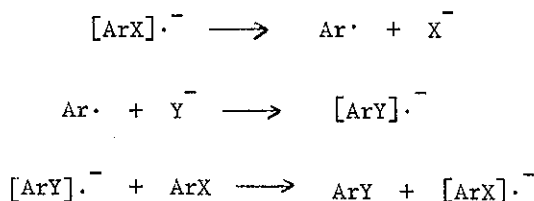
A radical chain mechanism must also involve initiation and termination steps, but, inasmuch as they are in some cases uncertain and possibly vary from case to case, they are not shown in Scheme I. This type of mechanism was first proposed for substitutions at some rather specialized aliphatic sites in 1966.[17,18] It was discovered as a mechanism of aromatic substitution in 1970.[2]

We now report some reactions of halothiophenes that probably occur by the $S_{RN}1$ mechanism.

Results

Reactions of 3-Bromothiophene (3) with Potassium Acetone Enolate (4).
As shown in Table I, reaction occurred in liquid ammonia under stimulation
either by photons or electrons to form one or more of five principal
products. The fundamental reaction of interest is that depicted in eq 1,
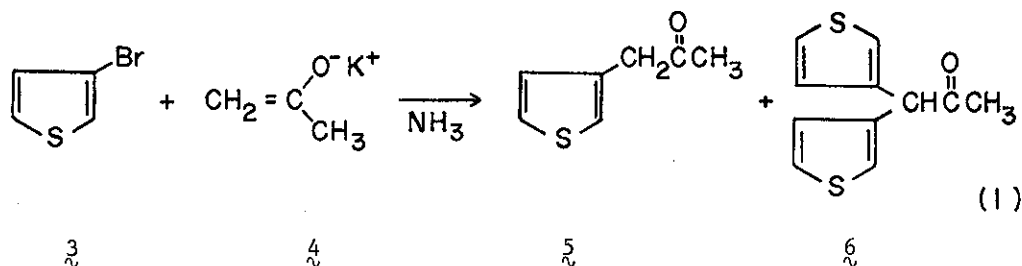
that is, the 3-thienylation of the enolate either once to form 5 or twice
to form 6. Other products that appear in most cases are thiophene (1), and
secondary alcohols 7 and 8 which are related to ketones 5 and 6, respectively.
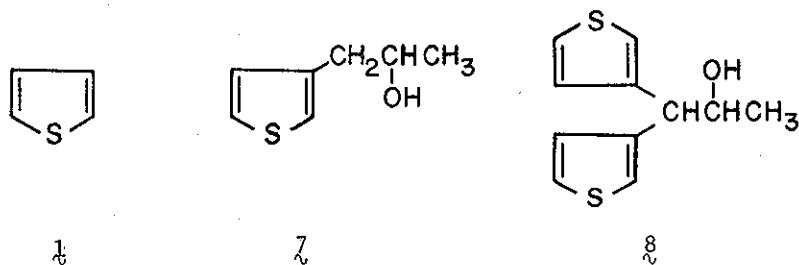
In Table I, the first experiment shows that, during one hour at -33°
in liquid ammonia, there was no reaction in the absence of stimulation by
photons or electrons. It should be noted, however, that reversible acid-
base reactions that did not afford further products would escape detection
by the methods we employed.

During an hour's irradiation by Pyrex-filtered light, 3 reacted with 4

Table I

Reactions of 3-Bromothiophene with Potassium Acetone Enolate in Liquid Ammonia

Expt. no.	Temperature, °C	[3], M	[4], M	Promoter, equiv.[a]	Reaction time, min.	Further component	Recovered 3, %	Products, %				
								1	5	7	6	8
1	-33	0.12	0.27	dark	60	t-BuOK, 0.09 M[b]	ca. 100					
2	-33	0.12	0.27	hν	60	t-BuOK, 0.09 M[b]	7	ca. 2	51		25	
3	-78	0.30	0.65	Na, 1.8	25	[c]	0	29	18	22	6	5
4	-78	0.25	0.54	Na, 1.8	20	NaBr, 0.5 M[c]	6	20	19	31	3	4
5	-78	0.25	0.53	Na, 1.9	20	Et$_4$N$^+$Br$^-$, 0.5 M[c]	0.3	5	22	32	4	3
6	-78	0.26	0.56	K, 1.8	15		0	29	29	23	5	2
7	-78	0.13	0.27	K, 1.8	7		0	5	28	22	10	4
8	-78	0.25	0.50	K, 1.8	10	KNH$_2$, 0.82 M	13	81				
9	-78	0.13	0.25	K, 1.8	7	KNH$_2$, 0.33 M	19	76				

[a] Moles of Na or K per mole of 3. [b] Also t-BuOH, 0.27 M. [c] Sodium benzoate added at end, before quenching.

(380)

to form monothienylation product $\underset{\sim}{5}$ in 51% yield and dithienylation product $\underset{\sim}{6}$ in 25% yield (Expt. 2). A small amount (7%) of $\underset{\sim}{3}$ remained unreacted, and 2% of debromination to thiophene occurred.

Experiments 3-7, inclusive, involve stimulation by sodium or potassium metal, which are sources of solvated electrons. In general, these reactions produced 20-30% yields of ketone $\underset{\sim}{5}$, representing monothienylation, and of the corresponding secondary alcohol ($\underset{\sim}{7}$). Smaller yields, in the range of 2-10%, of dithienylation products $\underset{\sim}{6}$ and $\underset{\sim}{8}$ were formed. In all cases there was some debromination to thiophene, and only in Expt. 4 was a little unreacted $\underset{\sim}{3}$ recovered.

Potassium amide was present in substantial concentration in Expts. 8 and 9, and it profoundly changed the character of the reaction. Only debromination was observed to occur, and recovery of unreacted $\underset{\sim}{3}$ was much greater than in Expts. 3-7.

Reactions of 2-Chlorothiophene (2a) and 2-Bromothiophene (2b) with Potassium Acetone Enolate (4). Our experimental observations are summarized in Table II. Equation 2 is a representation of most of them.
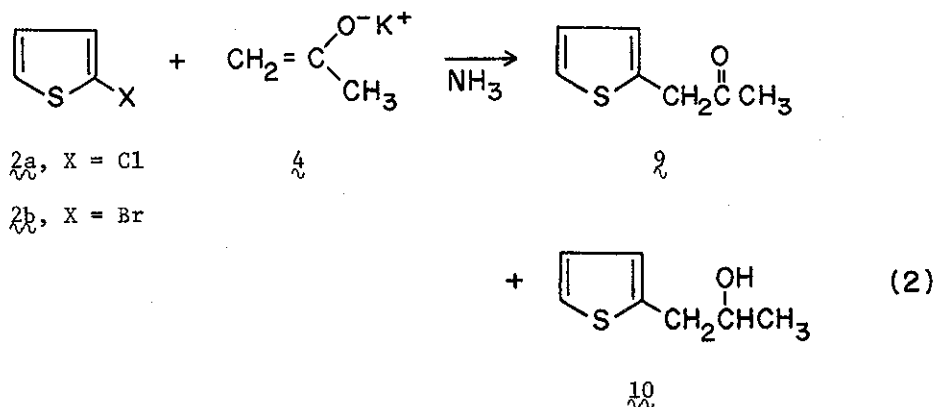

$$\underset{2a, \; X = Cl}{} \qquad \underset{2b, \; X = Br}{} \qquad \underset{4}{} \qquad \underset{5}{}$$

$$+ \qquad \underset{10}{} \qquad (2)$$

Table II

Reactions of 2-Chloro- and 2-Bromothiophene with Potassium Acetone Enolate in Liquid Ammonia

Expt. no.	Sub-strate	Temper-ature, °C.	Sub-strate concn., M	[4], M	Promoter, equiv.[a]	Reaction time, min.	Recovered substrate, %	Products, %				
								1	3	9	10	Other
11	2a	-78	0.27	0.60	dark	12	ca.100					
12	2a	-33	0.10	0.37[b]	hν	60	83		17			
13	2a	-78	0.33	0.70	Na, 2.4[c]	12		46		2	22	
14	2a	-78	0.16[d]	0.45	Na, 1.6	10	62	11			4	e
15	2a	-78	0.27	0.57	K, 1.7[c]	10	40	48			3	f
16	2a	-78[g]	0.33	0.68	K, 2.4[c]	20	12	54			8	
17	2b	-33	0.14	0.37[h]	dark	60	ca.100		0			
18	2b	-33	0.14	0.32[h]	hν	60	ca. 70	3	0	26		
19	2b	-33	0.14	0.32[h]	hν	60	44	5	0	31		
20	2b	-78	0.27	0.66	Na, 1.8[c]	10	ca. 5	74	8	1	1	i
21	2b	-78	0.26	0.55[j]	Na, 1.8[c]	15	2	70	10	ca.4	ca.3	
22	2b	-78	0.16[d]	0.44	Na, 1.7	10	k	31	23	0.7	3	ℓ
23	2b	-78	0.27	0.59	K, 1.8[c]	8		58				tar

[a]Moles of Na or K per mole of substrate. [b]Also present: t-BuOH, 0.37 M and t-BuOK, 0.08 M. [c]Sodium benzoate added at end, before quenching. [d]Substrate added dropwise to a mixture of 4 and Na metal in NH_3; blue color vanished halfway through addition. [e]2-(5-Chloro-2-thienyl)-2-propanol (11), ca. 23%. [f]Circa 3% of 11. [g]Temperature probably somewhat higher; the supply of solid CO_2 was exhausted during the experiment. [h]Also present: t-BuOH, with [t-BuOH] = [4], and t-BuOK, 0.05 M. [i]Small amounts of a dibromothiophene, a bromothienylpropanol and a dibromothienylpropanol. [j]NaBr, 0.5 M, also present. [k]Less than 16%. [ℓ]A dibromothiophene (ca.2%) and two isomeric 2-(bromothienyl)-2-propanols (sum ca.14%).

Experiments 11 and 17 indicate that no reaction occurs in the dark and without alkali metal stimulation. Experiments 12, 18, and 19 show that both 2a and 2b undergo photostimulated reaction with 4 to form 1-(2'-thienyl)-2-propanone, 9. Small amounts of thiophene were detected as a by-product in the experiments with 2b. In all three of these experiments substantial amounts of 2a or 2b were recovered. The reactivity of 2a and 2b in photo-stimulated reaction with 4 appears to be less than of 3; compare with Expt. 2, Table I.

The reactions of 2a or 2b with 4 and sodium or potassium metal afforded meager amounts of substitution products 9 and 10. Dehalogenation to thio-phene was extensive in many experiments. From some alkali metal experiments with 2a, substantial amounts of 2a were recovered. Little 2b was recovered from the alkali metal experiments with it, but there was appreciable forma-tion of its isomer, 3.

In two experiments, the order of combination of reagents was changed. Normally bits of Na or K metal were added to a solution of 2a or 2b and 4 in ammonia, but in Expts. 14 and 22 2a or 2b was added dropwise to a solu-tion of 4 and Na metal. In both these cases the blue color of the solvated electrons disappeared when about half the substrate had been added, but the addition of the amounts recorded in Table II was nevertheless completed. These experiments formed small amounts of alcohol 10 but larger amounts of 2-(halothienyl)-2-propanols such as 11a. This assignment of structure, rather than as halogen derivatives of 7 or 10, is based primarily on NMR spectra which differ greatly between 1-thienyl- and 2-thienyl-2-propanols.

Reactions of Bromothiophenes with Potassium Amide. Our observations are summarized in Table III.

Table III

Reactions of 2- and 3-Bromothiophene with KNH_2 in Liquid Ammonia at $-33°$

Expt. No.	Substrate	$[KNH_2]$, M	Atmo-sphere	Condi-tions	Reaction time, min.	Products, %			
						1	3	12	Other
31[a]	3	1.2	N_2	dark	60	4	12	79	
32	3	1.2	air	dark	60	3	44	2	tars
33[a]	3	1.2	N_2	hν	60	1	28	63	
34	2b	0.4	N_2	dark	15	9	37	48	b
35	2b	0.4	air	dark	15	12	43	31	b

[a] Average of two concordant runs.   [b] 3,4-Dibromothiophene, ca. 4%.
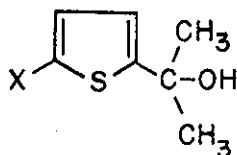
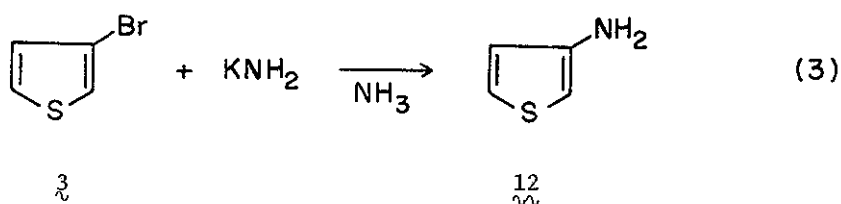11a, X = Cl

11b, X = Br

3-Bromothiophene (3) reacts with KNH_2 under an atmosphere of N_2 according to eq 3 to form, during one hour at $-33°$, 3-aminothiophene (12) in 79% yield. The latter was isolated as its acetyl derivative. There was also a little (4%) debromination to thiophene, and 12% of 3 was recovered unreacted.

Under an atmosphere of air (Expt. 32) the same reactants behaved very differently. Only 2% of 12 was obtained, and 44% of 3 was recovered.

$$\text{(structure 3: 3-bromothiophene)} \quad + \quad KNH_2 \quad \xrightarrow{NH_3} \quad \text{(structure 12: 3-aminothiophene)} \qquad (3)$$

3   12

There was a little debromination to thiophene, and much tar was formed. In

view of the instability of 12,[19] it is conceivable that 12 formed during

Expt. 32 was oxidized by the air in the system. We point out, however,

that air was only present above the reacting mixture, not bubbled through

it, and that we as well as other investigators[20,21] have been able to handle

12 in ordinary extraction operations without it suffering much decomposition.

Moreover, the fact that 44% of 3 was recovered unreacted from Expt. 32 shows

that the substitution reaction was genuinely slow compared to Expt. 31.

Observations on the reaction of 3 with KNH_2 in ammonia have been

reported by van der Plas, de Bie, Geurtsen, Reinecke, and Adickes.[21] They

found no reaction to occur at $-78°$, while the reaction at $-33°$ is described

in three experiments at varying proportions of KNH_2 to 3 as yielding 7-15%

of 12 and a little 3,4-dibromothiophene, and in two of the experiments

recovery of 3 was reported as 50 and 65%. The reported results considerably

resemble ours under air (Expt. 32) but differ sharply from ours under N_2

(Expt. 31). We could find no statement in the reports of those workers[21,22]

about the atmosphere that prevailed above the reaction of 3 with KNH_2.

In Expt. 33, the reaction of 3 with KNH_2 under N_2 was conducted in the

photochemical reactor. Under illumination the reaction behaves rather much

as in the dark (Expt. 31) but curiously it was slower, giving less 12 and

allowing more recovery of 3.

The reaction of 2-bromothiophene (2b) with 0.4 M KNH_2 under N_2 (Expt. 34) furnished 37% of 3-bromothiophene, which represents bromine migration, 48% of 3-aminothiophene (12), 9% of thiophene and a little of a dibromo-thiophene. The same reaction under air (Expt. 35) gave similar results, the minor differences being only that the yield of 12 was somewhat lower than under N_2 and of 3 a little higher. These results resemble those reported by other workers under similar conditions.[20-22]

Reactions with Other Nucleophiles. In experiments in this laboratory, Creary[23] examined briefly the reactions of 2-iodothiophene with ammonium thiophenoxide and with potassium diethyl phosphite, both under photostimu-lation. Both these reagents undergo photostimulated reaction with iodoben-zene to give high yields of substitution products.[10,11] With ammonium thiophenoxide there was a very slow reaction; after 2 hr irradiation, most of the 2-iodothiophene was recovered; a small amount of product that had formed appeared from its mass spectrum (m/e 192) to be phenyl 2-thienyl sulfide. Substantial reaction (91% iodide ion release) occurred during 2 hr irradiation with $(EtO)_2PO^-K^+$, but the only detectable volatile product was thiophene, and no unreacted 2-iodothiophene was found.

We irradiated a solution of 2b (0.1 M), potassium phenoxide (0.4 M) and KOH (0.1 M) in 50% aqueous t-butyl alcohol at 45° for 20 hr with "350 nm" light, but obtained no substitution product.

Discussion

Photostimulated Reactions with Acetone Enolate Ion. As reported in Table I, Expts. 1 and 2, 3-bromothiophene (3) undergoes satisfactory photo-stimulated reaction with potassium acetone enolate (4) according to eq 1, but no reaction occurs in the dark under similar conditions. The reaction resembles the photostimulated reaction of 4 with bromobenzene;[4] a point of

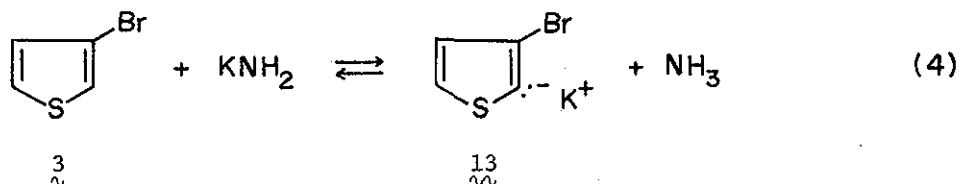difference is that relatively more diarylation occurs with 3 than with bromo-benzene.

There is considerable evidence that the reaction with bromobenzene occurs by the $S_{RN}1$ mechanism with the propagation sequence of Scheme I, Y^- being the acetone enolate ion.[4,7] We presume that the same mechanism obtains for the reaction of 3. The nature of the initiation and termination steps is unclear.

Experiments 12, 18, and 19, with reference to Expts. 11 and 17, Table II, show that 2-chloro- ($2a$) and 2-bromothiophene ($2b$) also react with 4 under the stimulus of light, forming 2-thienylacetone (9). $2b$ is somewhat more reactive than $2a$, just as bromobenzene is more reactive than chloro-benzene.[4] The reactivity of $2b$ is however distinctly lower than that of its isomer 3.

Because overall reactivity in a radical chain reaction is affected by reactivity in diverse initiation, propagation and termination steps, it is difficult to define whether the lesser reactivity of $2b$ than 3 is due to slowness in initiation, slowness in a key propagation step, or a greater rate of termination.

Electron-stimulated Reactions with Acetone Enolate Ion. The reaction of 3 with 4 under stimulation by Na or K metal in ammonia also resembles the corresponding reaction of bromobenzene. The prominent products are ketone 5 and the corresponding secondary alcohol, 7; see Expts. 3-7, Table I. There are, however, differences in detail. First, dithienylation to form ketone 6 and alcohol 8 is more prominent than with bromobenzene; indeed, 1,1-diphenyl-2-propanol has not been observed as a product of the electron-stimulated reaction of bromobenzene with 4. Furthermore, the proportion of secondary alcohol (7) to ketone (5) is higher than from the bromobenzene reaction.

Excess KNH$_2$ *completely suppresses arylation in favor of debromination;* see Expts. 8 and 9, Table I. The genesis of this striking effect, we think, is the acid-base reaction of eq 4. The acidity of H.2 in $\underset{\sim}{3}$ has been recog-

$$\text{(structure 3, thiophene with Br)} + KNH_2 \rightleftharpoons \text{(structure 13, thiophene with Br and } \cdot^- K^+) + NH_3 \qquad (4)$$

$$\underset{\sim}{3} \qquad\qquad\qquad\qquad \underset{\sim\sim}{13}$$

nized by other workers,[21] and the dearth of evidence that 2,3-thiophyne can be generated at ordinary temperatures[21,22,24] implies that $\underset{\sim\sim}{13}$ is unable to eject bromide ion to form an aryne. (We note, however, recent evidence for 2,3-thiophyne *as an intermediate in high temperature pyrolyses.*[25])

The pK$_a$ of H.2 in thiophene is estimated from measurements in cyclohexylamine solution[26] to be 38.4. For fluorine-substituted benzenes, measurements in the same solvent system indicate that the partial equilibrium *factor for ortho-fluorine is 5.7,* that is, that o-F decreases the pK$_a$ of aryl hydrogen by that amount.[27] Crudely, on the assumption that o-Br in the thiophene system has the same partial equilibrium factor as o-F in a benzene derivative, one reckons pK$_a$ for $\underset{\sim}{3}$ to be 32.7. Inasmuch as the pK$_a$ of *ammonia is 32.5,*[28] *and in view of the numerous assumptions involved, the* proposition that $\underset{\sim}{3}$ is extensively converted into $\underset{\sim\sim}{13}$ under the conditions of Expts. 8 and 9 is not unreasonable.

Why then should the transitory conversion of $\underset{\sim}{3}$ to $\underset{\sim\sim}{13}$ divert the whole *reaction from mainly carbanion thienylation to exclusive protodebromination,* with some $\underset{\sim}{3}$ surviving?

We suggest an hypothesis which involves three principal components. The first is that the rate of generation of 3-thienyl radicals from 13 is very much less than from 3. The second is that 3-thienyl radicals generated in the presence of both acetone enolate ions and solvated electrons combine preferentially with the latter, leading ultimately to thiophene. Combination with the enolate ion occurs preferentially only when the concentration of solvated electrons is very much lower. The two reaction pathways are sketched in Scheme II. The third component of the hypothesis is that in some cases a large fraction of the overall reaction occurs during the process of mixing.

Scheme II
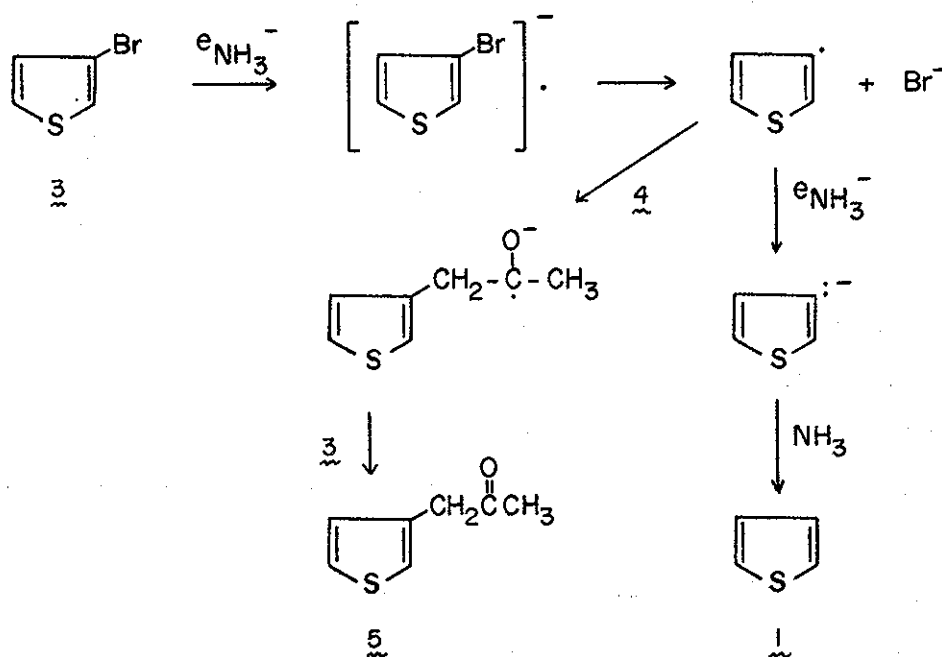
In terms of this hypothesis, the solution in Expt. 8 or 9 originally

containing 13 and 4 undergoes very little change during the process of

mixing with solvated electrons derived from the bits of K metal added during

the experiment. After mixing, molecular 3 is slowly released from 13 via

reaction 4, reverse, and converted by interaction with electrons to 3-

thienyl radical. The radical combines preferentially with a further electron

to form 3-thienyl anion and finally thiophene; see Scheme II.

In Expt. 3, 4, 5, 6, or 7, according to this hypothesis, the generation

of 3-thienyl radicals occurs rapidly during the process of mixing the solu-

tion of 3 and 4 with solvated electrons. As the two solutions are mixed,

there are initially zones rich in 3 and 4 and others rich in solvated elec-

trons, and boundaries between those zones. The boundaries are not neces-

sarily smooth; they may be ragged, with eddies from one zone swirling out

into the other. When molecules of 3 encounter solvated electrons, reaction

to form 3-thienyl radicals occurs very rapidly at the boundary, faster than

the process of mixing, and the radicals at the boundary have many oppor-

tunities to react with enolate ions rather than solvated electrons (of

which there are few at the boundary). Some radicals are captured by solvated

electrons, accounting for the appreciable amounts of thiophene produced

especially in Expts. 3, 4, and 6.

The electron-stimulated reactions of the 2-halothiophenes with 4 behave

quite differently; see Table II. With either 2a or 2b, only tiny amounts

of ketone 9 were formed, and except in Expt. 13 the yields of alcohol 10

were also very low. Dehalogenation to thiophene was extensive.

In terms of the hypothesis just presented, one could further hypothesize

that the radical anions of 2a and 2b are longer lived than of 3, so that

during mixing they mostly do not undergo scission to halide ion and

2-thienyl radical at the boundary between zones. A few do, accounting for

the formation of 9 and 10, but most break up only after being surrounded by

solvated electrons so that mainly thiophene is formed.

In the case of 2b, appreciable isomerization to 3 also occurred; see

Expts. 20-22, Table II. The base-catalyzed isomerization of 2- to 3-bromo-

thiophene, especially as catalyzed by sodium or potassium amide, is a well

recognized reaction;[21,22] it is a prominent example of the base-catalyzed

halogen dance.[30]

In Expts. 14 and 22, Table II, 2a or 2b was added to a solution of 4

and sodium metal, and in both the blue color of the dissolved metal

disappeared about half way through the addition of substrate. From these

experiments, besides products already discussed, there were obtained signif-

icant amounts of tertiary alcohols such as 11a from Expt. 14. We believe

11a to result from the addition of 5-chloro-2-thienyl anion to acetone, with

subsequent protonation. That small amounts of molecular acetone were present

in these systems is suggested by the fact that diacetone alcohol was a ubi-

quitous by-product. It is reasonable that 5-chloro-2-thienyl anion should

have been formed in the course of Expt. 14 but not in Expt. 11 because the

reaction of 2a with Na metal to form thiophene produces $NaNH_2$ as a by-product

whereas no reagent as basic as $NaNH_2$ was present in Expt. 11. The corre-

sponding experiment with 2b (Expt. 22) afforded a mixture of two tertiary

alcohols, probably 11b and 2-(3'-bromo-2-thienyl)-2-propanol, the former

derived directly from 2b and the latter from isomerization product 3.

Reactions with Potassium Amide. We found (Expts. 31 and 32, Table III)

that 3-bromothiophene reacts fairly rapidly with KNH_2 under an atmosphere of

N_2 to form 3-aminothiophene (eq 3), but that very little reaction occurs

under an atmosphere of air. These observations are consistent with the

radical chain $S_{RN}1$ mechanism. Inasmuch as neither electron nor photon stimulation was provided, some sort of thermal initiation process must have been involved. We do not know what it may be, but we do point out that the first recognition of aromatic substitution by the $S_{RN}1$ mechanism[2] involved reactions of some iodobenzene derivatives with KNH_2 at $-33°$ without electron or photon stimulation.

It is remarkable that the same reactants were less reactive under illumination with Pyrex-filtered light (Expt. 33). Conceivably the effective initiation process is insensitive to light, but illumination somehow produces a few radicals which act as chain terminators rather than initiators.

In a shorter time, 2-bromothiophene (2b) reacted completely with KNH_2 to form a mixture of 3 and 12 in proportions only slightly affected by changing the atmosphere from N_2 to air; see Expts. 34 and 35. That system has been studied extensively by other workers[21,22] who explain that the halogen migration occurs via di- or tribromothiophene intermediates and propose that the actual aminodebromination occurs in such an intermediate rather than in 3. Our results do not challenge that interpretation. They do suggest, however, that the $S_{RN}1$ mechanism must be seriously considered for aminodebromination reactions that occur on reaction of either mono- or oligobromothiophenes with KNH_2 in ammonia.

General Remarks. The present experiments show that 3-bromothiophene reacts quite well with acetone enolate ion and with amide ion, apparently by the $S_{RN}1$ mechanism, to form good yields of products representing nucleophilic substitution. We are cautiously optimistic that other $S_{RN}1$ reactions known for benzene derivatives[5-11] will also occur satisfactorily with 3 or with other thiophenes carrying nucleofugic substituents in the 3-position. If so, these reactions may provide useful synthetic entry into series of

3-substituted thiophenes that are hard to get by other means.[31]

Experience to date indicates $S_{RN}1$ reactions with 2-halothiophenes to be less successful.

Experimental Section

Materials. The samples of 2a, 2b, and 3 used were commercial products. GLC analysis showed the sample of 3 to contain 3% of 2b.

Analytical Methods. Except for 12, products were determined by GLC, with use of internal standards (benzene, diphenylmethane and/or chloro-benzene) and molar response factors. Molar response factors were determined experimentally for most products but were estimated for a few minor ones. Quantitative GLC was carried out with a column of 15% Carbowax 20M on Chromo-sorb P. Samples for spectral examination were isolated by preparative GLC on columns either of 10% Carbowax 20M on Chromosorb P or of 10% SE 30 sili-cone rubber on Chromosorb G. 3-Aminothiophene (12) was converted to its acetyl derivative (vide infra) which was isolated and weighed.

Standard Reaction Procedures. Each reaction was conducted in a three-neck, round-bottom flask fitted with a solid CO_2-isopropyl alcohol well-type condenser, stirred by a magnetic stirrer and constantly swept by a slow stream of dry N_2 (unless otherwise specified). Ammonia from a commercial cylinder was dried with K metal and distilled into the reaction flask.

For reactions with KNH_2, a weighed amount of potassium metal and a little ferric nitrate were added. After KNH_2 formation was complete, the solution was swirled so as to rinse back any K or KNH_2 deposited on the walls. The substrate was added all at once, in amount to provide 0.2 M concentration, and the mixture was stirred at reflux for times as listed in Table III. For reactions under air, the KNH_2 was formed under N_2 and the flask was then swept with dry air for 5 min. before addition of the substrate, as well as

during the reactions. Reaction was terminated by addition of excess NH_4Cl. Diethyl ether and internal standards were added and the ammonia was allowed to evaporate. For reactions under air, the system was again swept with N_2 after addition of NH_4Cl so as to exclude oxygen during evaporation of the ammonia. Water was added, the aqueous and ether phases were separated and the water layer extracted thrice with ether. The combined ether extracts were extracted four times with portions of 1 M aqueous HCl, then once with water, were dried over anhydrous Na_2SO_4 and analyzed by GLC. The combined aqueous HCl extracts were basified with NaOH and extracted four times with 50-ml portions of ether. To the combined ether extracts, 20 ml of acetic anhydride was added and the mixture was allowed to stand overnight at room temperature. The ether and excess acetic anhydride were removed on the rotary evaporator, and the residue was dried to constant weight at elevated temperature in vacuo.

For reactions with acetone enolate ion with irradiation, 4 was formed by addition of anhydrous t-BuOK to the ammonia, cooling to -78° and then addition of a quantity of acetone so as to leave t-BuOK in small excess, as noted in footnotes to Tables I and II. This procedure was also used for some dark reactions, as noted in Tables I and II. Irradiation was conducted in a Rayonet RPR-100 photochemical reactor equipped with 16 ca. 24-W fluorescent lamps emitting maximally at 350 nm. At termination of irradiation, excess NH_4Cl was added as well as internal standards and diethyl ether, and the ammonia was allowed to evaporate. Water was added, the two layers were separated, the aqueous phase was extracted with ether, and the combined ether fractions were washed with water, dried over anhydrous Na_2SO_4 and analyzed by GLC.

For alkali metal-stimulated reactions with 4, the enolate reagent was

generated (except as otherwise noted) by addition of an equimolar amount of acetone to KNH_2 in ammonia formed as described above. In some cases the resulting 4 was not fully in solution. The alkali metal was added in bits with stirring, the blue color from one bit being allowed to vanish before the next was added. Often, as noted in Tables I and II, sodium benzoate was added before addition of NH_4Cl. The subsequent procedure was as described immediately above. All the alkali metal-provoked reactions produced tars or dark solids insoluble in water, ether, or acetone, and in most product mixtures diacetone alcohol, identified by IR and NMR, was found in small amounts.

Product Identification. ·1-(3'-Thienyl)-2-propanone (5). NMR (neat) δ 1.97 (s, 3H), 3.58 (s, 2H), 6.88 (d of d, H.4, J_{45} 4.8 Hz, J_{24} 1.6 Hz), 7.0 (m, H.2), 7.17 (d of d, H.5, J_{45} 4.8 Hz, J_{25} 3.0 Hz). IR (neat) 630, 690, 710, 767, 834, 1160, 1215, 1240, 1315, 1350, 1385, 1410, 1710, 2925, 3000, 3100 cm^{-1}. MS m/e 140 (M^+), 98, 97 (100). n_D^{23} 1.5325 (lit.[32] n_D^{20} 1.5335).

1,1-Di(3'-thienyl)-2-propanone (6). NMR (CCl_4) δ 1.97 (s, 3H), 5.12 (s, 1H), 6.80-7.15 (m, 6H). IR (neat) 630, 650, 740, 770, 835, 1080, 1155, 1350, 1410, 1715, 2870-2900, 3105 cm^{-1}. MS m/e 222 (M^+), 179 (100).

1-(3'-Thienyl)-2-propanol (7). NMR (CCl_4) δ 1.10 (d, 3H, J 6.1 Hz), 2.65 (d, 2H, J 6.3 Hz), 3.57 (s, 1H, exchanges with D_2O), 3.88 (m, 1H), 6.75-7.15 (m, 3H). IR (neat) 630, 690, 770, 835, 854, 945, 1075, 1115, 1240, 1360, 1405, 1450, 2930, 2965, 3100, 3480, 3560 cm^{-1}. MS m/e 142 (M^+), 127, 99, 98, 97 (100). n_D^{23} 1.5355.

1,1-Di(3'-thienyl)-2-propanol (8). NMR (CCl_4) δ 1.02 (d, 3H, J 6.0 Hz), 2.40 (s, 1H, exchanges with D_2O), 4.02 (m, 2H), 6.75-7.15 (m, 6H). IR (neat)

630, 650, 740, 780, 840, 1075, 1110, 1250, 1390, 1405, 1450, 2895, 2925, 2975, 3100, 3425, 3550 cm^{-1}. MS $\underline{m/e}$ 181, 180, 179 (100), 147, 135, 120 (metastable, 180 → 147), 101.9 (metastable, 179 → 135).

1-(2'-Thienyl)-2-propanone (9). The NMR spectrum agreed with that reported by Campaigne and Johnson.[33] IR (neat) 698, 855, 1040, 1155, 1220, 1350, 1415, 1715, 2920, 3000, 3080, 3115 cm^{-1}. MS $\underline{m/e}$ 140 (M^+), 98, 97 (100). n_D^{23} 1.5325 (lit.[34] n_D^{20} 1.5347).

1-(2'-Thienyl)-2-propanol (10). NMR (CCl$_4$) δ 1.13 (d, 3H, J 6.0 Hz), 2.84 (d of d, 2H, J_{12} 6.5 Hz), 3.88 (m, 1H), 3.90 (s, 1H, exchanges with D$_2$O), 6.70-7.05 (m, 3H). IR (neat) 692, 812, 850, 933, 1070, 1110, 1200, 1245, 1365, 1430, 2940, 2980, 3380, 3560 cm^{-1}. MS $\underline{m/e}$ 142 (M^+), 127, 99, 98, 97 (100).

2-(5'-Chloro-2'-thienyl)-2-propanol (11a). NMR (CCl$_4$) δ 1.52 (s, 6H), 4.00 (s, 1H, exchanges with D$_2$O), 6.62 (s, 2H). IR (neat) 670, 795, 840, 945, 990, 1005, 1055, 1150, 1220, 1365, 1380, 1450, 2930, 2980, 3370 cm^{-1}. MS $\underline{m/e}$ 178 and 176 (M^+, weak), 160 and 158 (37 and 100), 145 and 143, 123, 108. The assignment of 2,5-orientation is based on the fact that the NMR absorption at δ 6.62 is a singlet, undoubtedly due to coincidental identity of chemical shifts of the two aryl protons, a situation more probable if they are at the 3- and 4-positions. The 2,5-orientation would also be expected from considerations of reaction mechanism.

2-(5'-Bromo-2'-thienyl)-2-propanol (11b) and 2-(3'-Bromo-2'-thienyl)-2-propanol. These were obtained from Expt. 22 (Table II) as a mixture inseparable on the SE 30 column. NMR (CCl$_4$) 1.52 (s) and 1.67 (s) (totaling 6H, in area ratio 5/7), 4.02 (s, 1H, exchanges with D$_2$O), 6.55-7.05 (m, 2H). The NMR spectrum of the 3'-bromo isomer in CDCl$_3$ has been reported[35] as δ 1.70 (CH$_3$), 2.97 (OH), 6.88 (H.4) and 7.03 (H.5), which accounts for the

signal we report at δ 1.67 and part of the aryl proton signal. IR (neat) 670, 710, 795, 835, 870, 945, 965, 1040, 1125-1160 (broad), 1220, 1340, 1360, 1435, 2930, 2975, 3400. However, the presumed bromothienylpropanol from Expt. 20 lacked IR absorption at 670, 795, 965, and 1040 cm^{-1}; of these all but that at 965 cm^{-1} appear in the IR spectrum of 11a. We therefore hypothesize that the sample from Expt. 22 contained a greater proportion of 11b than did the sample from Expt. 20. MS (from either experiment) m/e 222-220 (M^{+}), 207-205, 204-202, 189-187, 123, 108.

3-Aminothiophene (12). The isolation procedure described above furnished the acetyl derivative, of mp 141-143° or higher, raised by recrystallization from water to 146-147°, in agreement with literature values.[20]

3-Bromothiophene (3), recovered and as a product from 2b, was identified by the match of its IR spectrum with that of an authentic sample.

3,4-Dibromothiophene (from Expt. 34, Table III). IR 650, 780, 845, 905, 1110, 1325, 1395, 1475, 3120 cm^{-1}. MS m/e 244-242-240 (in ratio 1:2:1), 163-161, 119-117. The IR spectrum differed from those of authentic samples of 2,3- and 2,5-dibromothiophenes, and is in accord with the general IR behavior of 3,4-disubstituted thiophenes.[36] The complete absence of absorption between 930 and 1090 cm (9.17 and 10.75 μ) specifically disqualifies the 2,4-dibromothiophene possibility.[37]

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