mixture was stirred for 1.5 h at ambient temperature, diluted with water, and filtered. The gummy filter cake was recrystallized from ether to give 78 g (56%) of yellow, crystalline solid: ir (KBr) 3300 (NH) and 1150–1200 cm^{-1} (CF_3); NMR (Me_2SO-d_6) 7.5–8.5 (7, CH=) and 9.67 ppm (2, NH).

Registry No.—**2** (X = H; R_F = CF_3), 59872-52-5; **2** (X = H; R_F = C_3F_7), 736-62-9; **3** (X = H; R_F = CF_3), 54820-21-2; **3** (X = H; R_F = C_2F_5), 54820-24-5; **3** (X = H; R_F = C_3F_7), 59872-53-6; **3** (X = 2-F; R_F = CF_3), 59872-54-7; **3** (X = 4-Cl; R_F = CF_3), 59872-55-8; **3** (X = 4-Cl; R_F = C_2F_5), 59872-56-9; **3** (X = 4-Cl; R_F = C_3F_7), 59872-57-0; **3** (X = 3,4-Cl_2; R_F = CF_3), 59872-58-1; **3** (X = 3-CF_3; R_F = CF_3), 59872-59-2; **3** (X = 3-CH_3; R_F = CF_3), 59872-60-5; **3** (X = 4-CH_3; R_F = CF_3), 59872-61-6; **3** [X = 3,4-$(CH_3)_2$; R_F = CF_3], 59872-62-7; **3** [X = 3,5-$(CH_3)_2$; R_F = CF_3], 59872-63-8; **3** [X = 3,5-$(CH_3)_2$-4-Cl; R_F = CF_3], 59872-64-9; **3** [X = 4-$C(CH_3)_3$; R_F = CF_3], 59872-65-0; **3** (X = 4-NO_2; R_F = CF_3), 59872-66-1; **3** (X = 3,4-CH=CHCH=CH; R_F = CF_3), 59872-67-2; **7** (X = H; R_F = CF_3), 54820-22-3; **7** (X = H; R_F = C_2F_5), 59872-68-3; **7** (X = H; R_F = C_3F_7), 59872-69-4; **7** (X = 2-F; R_F = CF_3), 59872-70-7; **7** (X = 4-Cl; R_F = CF_3), 59872-71-8; **7** (X = 4-Cl; R_F = C_2F_5), 59872-72-9; **7** (X = 4-Cl; R_F = C_3F_7), 59872-73-0; **7** (X = 3,4-Cl_2; R_F = CF_3), 59872-74-1; **7** (X = 3-CF_3; R_F = CF_3), 59872-75-2; **7** (X = 3-CH_3; R_F = CF_3), 59872-76-3; **7** (X = 4-CH_3; R_F = CF_3), 59872-77-4; **7** [X = 3,4-$(CH_3)_2$; R_F = CH_3], 59872-78-5; **7** [X = 3,5-$(CH_3)_2$; R_F = CF_3], 59872-79-6; **7** [X = 3,5-$(CH_3)_2$-4-Cl; R_F = CF_3], 59872-80-9; **7** [X = 4-$C(CH_3)_3$; R_F = CF_3], 59872-81-0; **7** (X = 4-NO_2; R_F = CF_3), 59872-82-1; **7** (X = 3,4-CH=CHCH=CH; R_F = CF_3), 59872-83-2; **10** (X = H), 613-94-5; **10** (X = 2-F), 446-24-2; **10** (X = 4-Cl), 536-40-3; **10** (X = 3-CH_3), 13050-47-0; **10** [X = 3,5-$(CH_3)_2$], 27389-49-7; **10** [X = 4-$C(CH_3)_3$], 43100-38-5; **10** (X = 2-Cl), 5814-05-1; **10** (X = 3,4-Cl_2), 28036-91-1; **10** (X = 4-NO_2), 636-97-5; **10** (X = 3-CF_3), 22227-25-4; **10** [X = 3,5-$(CF_3)_2$], 26107-82-4; **10** (X = 3,4-CH=CHCH=CH), 39627-84-4; hydrazine, 302-01-2; methylhydrazine, 60-34-4; 1,2-dimethylhydrazine, 540-73-8; trifluoroacetaldehyde, 75-90-1; pentafluoropropionaldehyde methyl hemiacetal, 59872-84-3; heptafluorobutyraldehyde ethyl hemiacetal, 356-26-3; trifluoroacetyl chloride, 354-32-5; benzalhydrazone, 5281-18-5; heptafluorobutyric acid hydrazide, 1515-05-5; benzaldehyde, 100-52-7.

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Smiles Rearrangement of 2-Tetrazolylthio-3-aminopyridines

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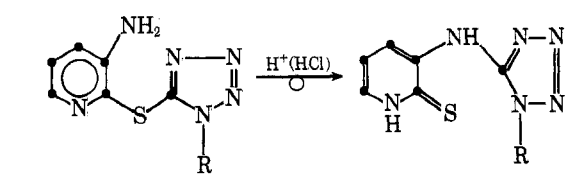
Received March 26, 1976

The Smiles rearrangement of 2-tetrazolylthio-3-aminopyridines **1** that contain alkyl and aralkyl substituents on the tetrazole moiety occurs under acidic conditions in refluxing ethanol to yield 2-mercapto-3-tetrazolylaminopyridines **2**. Under the same conditions, hydrazoic acid is eliminated to yield the corresponding 2-anilinothiazolo[5,4-*b*]pyridine **3** when the tetrazole moiety contains an aryl group. The synthesis of the 2-tetrazolylthio-3-aminopyridines and a plausible mechanism for both the Smiles rearrangement and the 2-anilinothiazolo[5,4-*b*]pyridine formation are discussed. Structure proofs for a 2-mercapto-3-tetrazolylaminopyridine and a 2-anilinothiazolo[5,4-*b*]-pyridine are presented. Rearrangements involving a migrating tetrazole ring and a new example of the collapse of a Smiles rearrangement cyclic transition state to form a new heterocyclic ring are demonstrated.

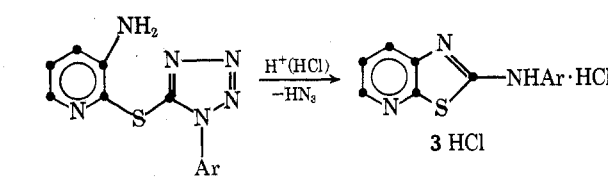
The Smiles rearrangement is an intramolecular nucleophilic aromatic substitution.[1,2] The scope of this reaction increases as more papers describing this rearrangement of a diversity of molecular systems are being published. Smiles recognized that certain diaryl sulfides undergo an intramolecular nucleophilic reorganization under alkaline conditions.[3] Since then, extensive investigations of these isomerizations of diaryl sulfides have been pursued.[1] Later, Maki extended the study of the Smiles rearrangement to phenylpyridyl sulfides[4] and to dipyridyl sulfides.[5] Rodig et al. then showed that this rearrangement of dipyridyl sulfides can occur under acidic as well as basic conditions.[6] This transformation of certain heterocyclic sulfides followed by ring closure has led to some interesting tricyclic ring systems.[7,8] Smiles-type rearrangements in which the migrating aryl ring loses a molecular fragment while the cyclic transition state forms a new ring have been reported.[9,10] The cyclic transition state for this rearrangement, however, has also been trapped as a stable cyclic Meisenheimer complex.[11] Thus far, few examples of Smiles rearrangements of migrating aryl groups containing more than one heteroatom have appeared.[8-10,12-14]

This paper describes the successful acid-promoted Smiles



(1)

1 2

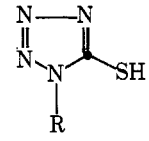


(2)

1 3 HCl

rearrangement of 2-tetrazolylthio-3-aminopyridines **1** to the corresponding 2-mercapto-3-tetrazolylaminopyridines **2** (reaction 1). Furthermore, when the R substituent is an aryl group, the elimination of hydrazoic acid occurred under the same acidic conditions to form the corresponding 2-anilinothiazolo[5,4-*b*]pyridine **3** (reaction 2). Previously, an attempted Smiles rearrangement of a phenyltetrazolyl thiohy-

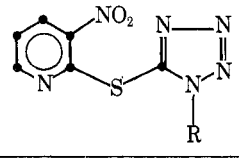
Table I. 1-Substituted 5-Mercaptotetrazoles



Registry no.	R	Yield, %	Mp, °C	Lit. mp, °C
13183-79-4	CH_3	60	121–122	125–126[15]
15217-53-5	C_2H_5	54	45–46	50[15]
42770-71-8	n-C_4H_9	70	37–38	40–41[16]
7624-33-1	CH_2=$CHCH_2$	28	66–67	69[15]
33898-72-5	$C_6H_5CH_2$	48	141–142	144[15]
59888-15-2	$C_6H_5CH_2CH_2$[a]	34	100–101[b]	
14331-22-7	1-Naphthyl	41	148–149	155–160[17]
1544-79-2	4-FC_6H_4	25	155–156	154–155[15]

[a] Gave a satisfactory C, H, N analysis. [b] Crystallized from ethyl ether–ligroin (bp 30–60 °C).

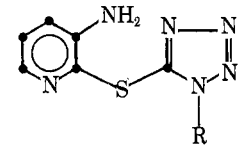
Table II. 2-Tetrazolylthio-3-nitropyridines



Registry no.	R	Yield, %	Mp, °C[a,b]
59888-16-3	CH_3	88	184–185
59888-17-4	C_2H_5	82	163–164
59938-98-6	n-C_4H_9	63	81–82
59888-18-5	CH_2=$CHCH_2$	76	125–126
59888-19-6	$C_6H_5CH_2$	81	138–139
59888-20-9	$C_6H_5CH_2CH_2$	84	111–112
59888-21-0	C_6H_5[c]	60	176–177[d]
59888-22-1	1-Naphthyl	96	200–201[d]
59888-23-2	4-FC_6H_4	70	189–190[d]

[a] All compounds were crystallized at least once from ethanol except the n-butyl compound which was crystallized from ethyl acetate. [b] All compounds gave satisfactory C, H, N analyses except as noted. [c] Anal. Calcd for $C_{12}H_8N_6O_2S$: C, 48.0; H, 2.7; N, 28.0. Found: C, 47.7; H, 2.6; N, 28.5. [d] Decomposed while melting.

Table III. 2-Tetrazolylthio-3-aminopyridines



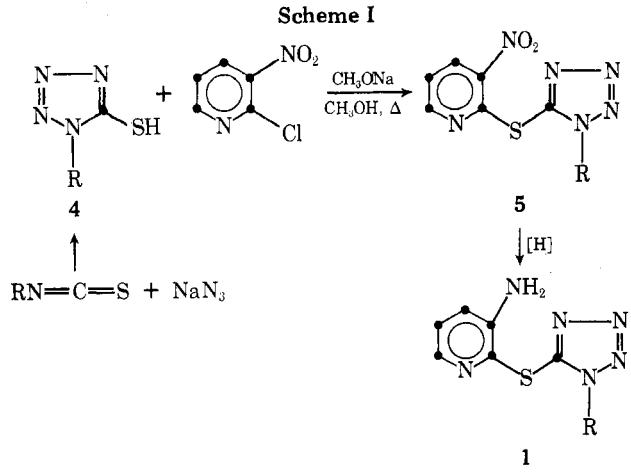
Registry no.	R	Yield, %	Mp, °C	Method[a,b]
59888-24-3	CH_3	54[c]	124–125	A
59888-25-4	C_2H_5	23[d]	77–78	B
59888-26-5	n-C_4H_9[e]	46[d]	108–109	B
59888-27-6	CH_2=$CHCH_2$	55[f]	66–67	A
59888-28-7	$C_6H_5CH_2$	16[d]	140–141	A
59888-29-8	$C_6H_5CH_2CH_2$	55[d]	133–134	A
59888-30-1	C_6H_5	32[c]	135–136[g]	B
59888-31-2	1-Naphthyl	39[d]	149–150[g]	B
59888-32-3	4-FC_6H_4	29[c]	131–133[g]	B

[a] See text. [b] All compounds gave satisfactory C, H, N analyses except as noted. [c] Crystallization from ethanol. [d] Crystallization from ethyl acetate. [e] Anal. Calcd for $C_{10}H_{14}N_6S$: C, 48.0; H, 5.6; N, 33.6. Found: C, 47.5; H, 5.5; N, 33.4. [f] Crystallized from ethyl ether. [g] Decomposed while melting.

drazonate resulted in a cleavage reaction to yield 1-phenyl-5-mercaptotetrazole.[14]

A series of 2-tetrazolylthio-3-aminopyridines was prepared according to Scheme I. The 1-substituted 5-mercaptotetrazoles 4 were prepared by refluxing the appropriately substituted isothiocyanates with excess sodium azide in aqueous solution (Table I). These mercaptotetrazoles, with 1 equiv of sodium methoxide in methanol solution, readily condensed with 2-chloro-3-nitropyridine under reflux conditions to give the corresponding 2-tetrazolylthio-3-nitropyridines 5 as pale yellow crystalline solids (Table II). Reduction of the nitro group to the amino group was achieved either by treatment with tin(II) chloride in concentrated hydrochloric acid (method A) or by catalytic hydrogenation using 10% palladium/charcoal in ethanol (method B). Table III summarizes the 2-tetrazolylthio-3-aminopyridines obtained by both methods.

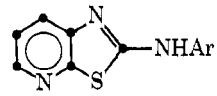
Scheme I



Experimental conditions under which the Smiles rearrangement of 1 occurred were then sought. When 1 (R = C_6H_5) was refluxed in absolute ethanol, only unchanged starting material was recovered. When this 2-tetrazolylthio-3-aminopyridine was refluxed in ethanol that contained a few drops of hydrochloric acid, however, 2-anilinothiazolo[5,4-b]pyridine 3 (Ar = C_6H_5) was isolated (as its hydrochloride) instead of the exected 2-mercapto-3-tetrazolylaminopyridine 2 (R = C_6H_5). When 1 (R = C_6H_5) was refluxed in ethanolic potassium hydroxide, the same bicyclic compound was found. The acid-promoted reaction appeared to be much cleaner and gave higher yields of product.

The rest of the compounds in Table III were subjected to the same acidic reaction conditions to determine the generality of this thiazolopyridine synthesis. When R was an aryl group, the corresponding 2-anilinothiazolopyridine 3 was formed (Table IV). When R was an alkyl or an aralkyl group,

Table IV. 2-Anilinothiazolo[5,4-*b*]pyridines[a]



Registry no.	Ar	Yield, %	Mp, °C
59922-51-9	C_6H_5	84[b]	180–181
59888-33-4	4-FC_6H_4	50[c]	209–210
59888-34-5	1-Naphthyl	54[b]	174–175

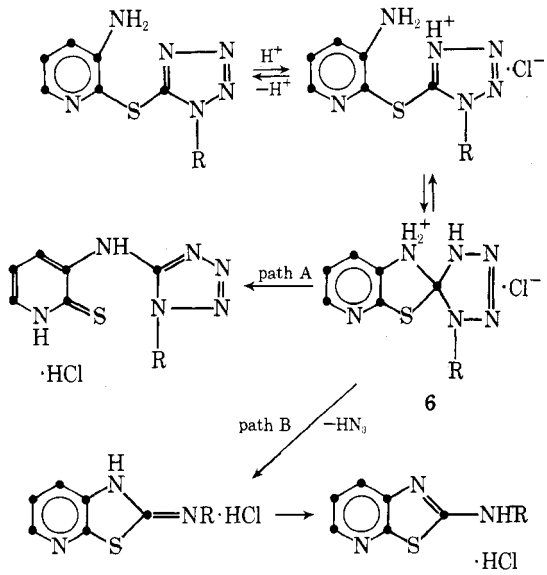
[a] All compounds gave satisfactory C, H, N analyses. [b] Crystallized from ethyl acetate. [c] Crystallized from ethanol.

the normal Smiles rearrangement occurred since the isomeric 2-mercapto-3-tetrazolylaminopyridine **2** was formed (Table V).

Discussion

A reasonable mechanism (Scheme II), involving a common intermediate **6**, may be proposed for the two divergent reac-

Scheme II

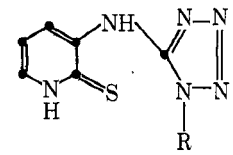


tion pathways exhibited by the 2-tetrazolylthio-3-aminopyridines in refluxing ethanolic hydrochloric acid. The elimination of hydrazoic acid from the proposed spiro intermediate **6** is probably dependent on the ability of the R substituent to stabilize either the free radical or more likely the charged species that results. When R is an alkyl or an aralkyl substituent, the transition state energy required for path B is apparently quite high, and path A, which leads to the normal Smiles rearrangement product, is favored. When R is an aryl substituent, the transition state energy for path B is lowered enough so that this pathway predominates. A diradical species, resulting after the elimination of hydrazoic acid, cannot be definitely excluded at this time.

When **1** (R = C_6H_5) was refluxed in ethanolic hydrochloric acid for 18 h, the hydrochloride salt of **3** was the principal product. The filtrate, after removal of this precipitated **3** HCl, was found by mass spectrometry to consist of additional **3** HCl plus a molecular ion with *m/e* 270. By comparing the fragmentation pattern of this ion with that of pure **1** (R = C_6H_5), an unequivocal assignment of this species to either **1** or **2** could not be made. Whether the normal Smiles rearrangement (**1** → **2**) may occur to a small extent when **1** (R = aryl) is subjected to these acidic reaction conditions is currently being investigated.

When **1** (R = CH_3) was refluxed in ethanolic hydrochloric acid for 18 h, **2** (R = CH_3) was the major product (>95%) found by mass spectrometry.

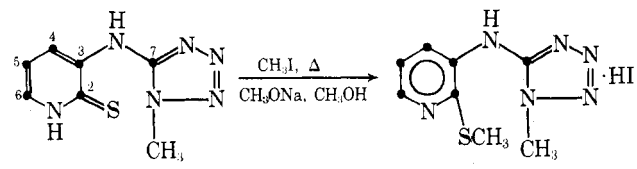
Table V. 2-Mercapto-3-tetrazolylaminopyridines



Registry no.	R	Yield, %	Mp, °C[a,b]
59888-35-6	CH_3	46[c]	217–218
59888-36-7	C_2H_5[d]	9[e]	201–202
59888-37-8	*n*-C_4H_9	34[e]	190–191
59888-38-9	CH_2=$CHCH_2$	37[e]	191–192
59888-39-0	$C_6H_5CH_2$	50[e]	210–211
59888-40-3	$C_6H_5CH_2CH_2$	60[f]	208–209

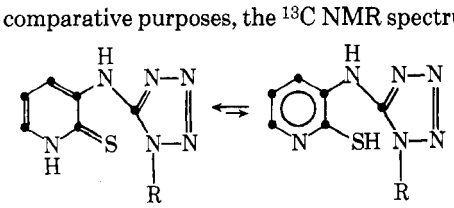
[a] All compounds melted with decomposition. [b] All compounds gave satisfactory C, H, N analyses except as noted. [c] Crystallized from absolute ethanol. [d] Anal. Calcd for $C_8H_{10}N_6S$: C, 43.2; H, 4.5; N, 37.8. Found: C, 43.6; H, 4.6; N, 38.3. [e] Crystallized from ethyl acetate. [f] Crystallized from ethyl acetate–ethanol.

Evidence for the Smiles rearrangement to structure **7** when **1** (R = CH_3) was refluxed in ethanolic hydrochloric acid has been obtained. The 2-mercapto group of **7** was easily converted to its thiomethyl ether **8** with iodomethane and sodium



7 **8** (3)

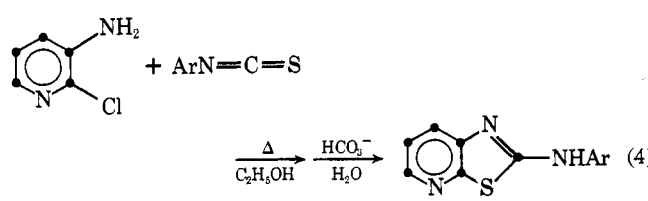
methoxide in refluxing methanol (reaction 3). The thiomethyl carbon of **8** exhibited a ^{13}C NMR resonance at δ 12.828 ppm.[18] Furthermore, the ^{13}C NMR spectrum of **8** showed a resonance for the *N*-methyl carbon at δ 32.549 ppm.[19] The ^{13}C NMR spectrum of **7** showed a resonance at δ 166.166 ppm which was assigned to the 2-thionecarbon atom,[18] while the *N*-methyl carbon resonated at δ 32.369 ppm. The 2-carbon atom resonance of **7** was shifted upfield to δ 153.699 or 153.219 ppm (one value was for C-2, the other for C-7) in compound **8**. These values strongly suggested that **2** exists in the pyridine-2(1*H*)-thione form rather than in the tautomeric thiol form **2a**. For comparative purposes, the ^{13}C NMR spectrum of **1** (R



2 **2a**

= CH_3) revealed a C-2 resonance at δ 149.862 ppm and an *N*-methyl carbon resonance at δ 34.108 ppm.

Thiazolopyridine structure **3** was firmly established by an independent synthesis (reaction 4).[20a,b] The thiazolopyridines **3** (Ar = C_6H_5) obtained by the two different routes (reactions 2 and 4) were identical in all respects.



3 (4)

Conclusions

2-Tetrazolylthio-3-aminopyridines **1** that contain alkyl or aralkyl substituents on the tetrazole moiety undergo the normal Smiles rearrangement to 2-mercapto-3-tetrazolylaminopyridines **2** in refluxing ethanolic hydrochloric acid. The 2-tetrazolylthio-3-aminopyridines studied that contain aryl groups on the tetrazole eliminate hydrazoic acid under these acidic conditions to yield 2-anilinothiazolo[5,4-*b*]pyridines **3**. These different reaction pathways are probably due to the stability of spiro intermediate **6**. The elimination of hydrazoic acid from this spiro intermediate is a new example of a Smiles rearrangement cyclic transition state that loses a molecular fragment to form a new heterocyclic ring. Furthermore, a successful Smiles rearrangement involving a migrating tetrazolyl ring has been demonstrated.

The Smiles rearrangement of other systems that have heterocyclic rings containing at least two heteroatoms is currently being investigated.

Experimental Section[21]

Materials. 1-Phenyl-5-mercapto-1*H*-tetrazole, phenyl isothiocyanate, methyl isothiocyanate, ethyl isothiocyanate, *n*-butyl isothiocyanate, allyl isothiocyanate, benzyl isothiocyanate, 2-phenethyl isothiocyanate, and 1-naphthyl isothiocyanate were Eastman grade compounds. The other compounds, 4-fluorophenyl isothiocyanate, 2-chloro-3-nitropyridine, and 2-chloro-3-aminopyridine, were obtained from the Aldrich Chemical Co.

General Mercaptotetrazole (4) Synthesis[15] Illustrated for 1-(2-Phenethyl)-5-mercapto-1*H*-tetrazole. A stirred aqueous mixture (400 ml) of 2-phenethyl isothiocyanate (40.8 g, 0.250 mol) and sodium azide (24.4 g, 0.375 mol) was refluxed for 6 h. When cool, this aqueous mixture was extracted with two portions of diethyl ether. With ice cooling, the aqueous phase was carefully acidified with concentrated hydrochloric acid, and was then extracted with two portions of diethyl ether. The combined ether extract was washed with distilled water, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residual colorless solid was crystallized from ethyl ether–ligroin (bp 30–60 °C) to 17.5 g (34%) of colorless crystals. The mercaptotetrazoles described in this paper are presented in Table I.

Representative 2-Tetrazolylthio-3-nitropyridine (5) Synthesis Illustrated for 2-[5-[1-(2-Phenethyl)-1*H*-tetrazolyl]thio]-3-nitropyridine. To a stirred methanol solution (100 ml) of 1-(2-phenethyl)-5-mercapto-1*H*-tetrazole (10.0 g, 0.0485 mol) and sodium methoxide (2.6 g, 0.0485 mol) was added 2-chloro-3-nitropyridine (7.7 g, 0.0485 mol). The resultant stirred solution was refluxed for 16 h and the methanol was removed from the cooled mixture under reduced pressure. The residue was partitioned between chloroform and distilled water, and the chloroform extract was dried over magnesium sulfate. After the solvent was removed under reduced pressure, the residual yellow solid was crystallized from ethanol to yield 13.4 g (84%) of pale yellow prisms. Analytical data for the 2-tetrazolylthio-3-nitropyridines discussed in this paper are summarized in Table II.

Representative 2-Tetrazolylthio-3-aminopyridine (1) Synthesis Illustrated for 2-[5-[1-(2-Phenethyl)-1*H*-tetrazolyl]-thio]-3-aminopyridine (Method A). To a stirred concentrated hydrochloric acid solution (55 ml) of $SnCl_2 \cdot 2H_2O$ (41.3 g, 0.183 mol) was added the corresponding 2-tetrazolylthio-3-nitropyridine (12.0 g, 0.0366 mol) over a 2-h period. The temperature of the stirred mixture was never allowed to exceed 50 °C. This stirred mixture was kept at ambient temperature for 21 h and then was transferred to a 2-l. Erlenmeyer flask. Distilled water (50 ml) and chloroform (200 ml) were added to this mixture, and the resultant slurry was made alkaline with sodium carbonate (1 equiv) and concentrated ammonium hydroxide. After the suspension was removed by filtration through a fritted flask filter, the filtrate was extracted with two portions of chloroform, and the combined chloroform extract was washed with a small amount of distilled water. The chloroform extract was then dried over magnesium sulfate. After the solvent was removed under reduced pressure, the residual solid was crystallized from ethyl acetate to yield 6.0 g (55%) of colorless needles (Table III).

Representative 2-Tetrazolylthio-3-aminopyridine (1) Synthesis Illustrated for 2-[5-(1-Phenyl-1*H*-tetrazolyl)thio]-3-aminopyridine (Method B). A mixture of the corresponding 2-tetrazolylthio-3-nitropyridine (10.5 g, 0.035 mol) and 10% palladium/charcoal (3 g) in ethanol (200 ml) was treated with hydrogen (3 atm) at ambient temperature for 30 h. The catalyst was removed by filtration and the filtrate was concentrated to ca. one-half volume. The precipitated colorless, silky needles were collected and dried, yield 3.0 g, 32% (Table III).

Representative 2-Mercapto-3-tetrazolylaminopyridine (2) or 2-Anilinothiazolo[5,4-*b*]pyridine (3) Synthesis Illustrated for 2-Mercapto-3-[5-[1-(2-Phenethyl)-1*H*-tetrazolyl]amino]-pyridine. A stirred solution of the corresponding 2-tetrazolylthio-3-aminopyridine (4.0 g, 0.0134 mol) and concentrated hydrochloric acid (10 ml) in ethanol (100 ml) was refluxed for 18 h. After the coled solution was concentrated to ca. one-half volume and the concentrate was chilled for 66 h, the precipitated yellow solid was collected by filtration and washed with ethanol. This solid was partitioned between dilute ammonium hydroxide and chloroform. After the chloroform extract was washed with distilled water and the extract was dried over magnesium sulfate, the solvent was removed under reduced pressure. The crystalline residue was crystallized from ethyl acetate–ethanol to yield 2.4 g (60%) of pale yellow prisms. The 2-mercapto-3-tetrazolylaminopyridines and the 2-anilinothiazolo[5,4-*b*]pyridines discussed in this paper are listed respectively in Tables V and IV.

2-Methylthio-3-[5-(1-methyl-1*H*-tetrazolyl)amino]pyridine Hydriodide (8). To a stirred suspension of 2-mercapto-3-[5-(1-methyl-1*H*-tetrazolyl)amino]pyridine (2.1 g, 0.01 mol) and sodium methoxide (0.54 g, 0.01 mol) in methanol (25 ml) was added iodomethane (1.4 g, 0.01 mol). This stirred suspension was refluxed for 66 h and, after cooling, the methanol was removed under reduced pressure. The residue was suspended in hot ethanol and undissolved solid was removed by filtration. A crystalline solid separated from the chilled filtrate: yield 0.3 g (9%); mp 184–185 °C dec; MS *m/e* 222 ($C_8H_{11}IN_6S$ − HI); ^1H NMR δ 2.53 (s, 3 H, $-SCH_3$), 3.92 (s, 3 H, NCH_3), 7.22 (dd, $J \simeq 9, 9$ Hz, 1 H), 7.80 (dd, $J \simeq 9, 2$ Hz, 1 H), and 8.37 (dd, $J \simeq 6, 2$ Hz, 1 H); ^{13}C NMR δ 12.828 ($-SCH_3$), 32.549 (NCH_3), 153.219 and 153.699 (C-2, C-7 carbons).

Anal. Calcd for $C_8H_{11}IN_6S$: C, 27.4; H, 3.1; N, 24.0. Found: C, 27.5; H, 3.2; N, 23.9.

Independent Synthesis of 2-Anilinothiazolo[5,4-*b*]pyridine.[20b] A stirred mixture of 2-chloro-3-aminopyridine (2.0 g, 0.016 mol) and phenyl isothiocyanate (2.2 g, 0.016 mol) was refluxed in ethanol (15 ml) for 18 h. After the resultant yellow suspension was chilled, the solid was collected and dried, yield 2.4 g (57%) of the hydrochloride. The base was liberated with aqueous sodium bicarbonate and was crystallized from ethyl acetate, mp 179–180 °C. A mixture melting point with a sample obtained by the elimination of hydrazoic acid from the appropriate 2-tetrazolylthio-3-aminopyridine (vide supra) was undepressed.

Acknowledgment. Stimulating discussions with Professor H. Suschitzky (University of Salford, England) are gratefully acknowledged. D. P. Maier and R. S. Gohlke determined the mass spectra, while T. H. Regan and R. L. Young measured the NMR spectra. The elemental analyses were performed by G. N. Meyer and his staff at the Kodak Research Laboratories.

Registry No.—**8**, 59888-41-4; phenethyl isothiocyanate, 2257-09-2; 2-chloro-3-nitropyridine, 5470-18-8; 2-chloro-3-aminopyridine, 6298-19-7; phenyl isothiocyanate, 103-72-0.

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Oxidations by Thionyl Chloride. 8. A Convenient Synthesis of Benzo[*b*]thiophenes from Carboxylic Acids and Ketones[1,2]

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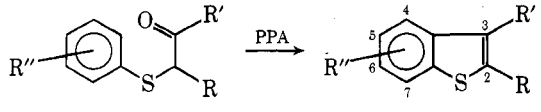
Received May 13, 1976

Benzo[*b*]thiophenes are prepared in one step from cinnamic acids, hydrocinnamic acids, or certain ketones plus thionyl chloride and pyridine. Para-substituted cinnamic acids gave rise to benzo[*b*]thiophenes in 41–69% yields together with α-chlorocinnamic acid derivatives. 3-Substituted 3-phenylpropanoic acids gave 3-aryl- or -alkyl benzo[*b*]thiophenes in 77% (3-H) to 16% (3-CH_3) yield; in the latter case, uncyclized sulfenyl chloride was also found. Ketones of the type $PhCH_2CH_2COR$ gave benzo[*b*]thiophenes in 52% (R = Ph) and 68% (R = *tert*-butyl) yields. An alternative two-step synthesis from 3-substituted 3-phenylpropanoic acids via cyclization of sulfenyl chloride **11** furnished benzo[*b*]thiophenes in 61% (3-H) and 66% (3-CH_3) yields, but only 2-chloro-1-phenylinden-3-one (**13**) and 1-oxoindeno[2,3-*d*]benzo[*b*]thiophene (**14**) in 12 and 63% yields, respectively (3-Ph). The indenones were also prepared by Friedel–Crafts cyclization of the sulfenyl chlorides derived from cinnamic acids.

Among a number of synthetic methods known[3,4] for the preparation of benzo[*b*]thiophenes, cyclodehydration of aryl sulfides (for example, arylthio acetones, eq 1) is the most



(1)

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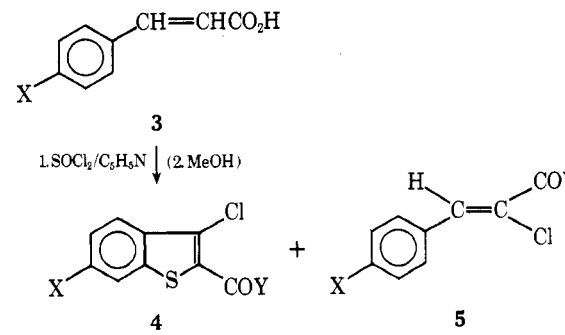
common and widely practiced method. This method unambiguously affords 5- and 7-substituted benzo[*b*]thiophenes from para- and ortho-substituted phenyl sulfides, respectively, but mixtures of 4- and 6-substituted benzo[*b*]thiophenes result from meta-substituted starting materials. In this method, preparation of starting materials usually requires a several-step sequence of reactions.

On the other hand, as evident from a previous paper,[5] if the reaction of thionyl chloride with cinnamic acids or 3-arylpropanoic acids can be generally applied, it would furnish 4- and 6-substituted benzo[*b*]thiophenes from ortho- and para-substituted starting materials, respectively, and 5- and 7-substituted benzo[*b*]thiophenes from meta-substituted starting materials. Thus the reaction would offer a convenient method for the preparation of benzo[*b*]thiophenes not only by supplementing the cyclodehydration methods, but also by being a one-step synthesis. We now describe a synthetic application of the thionyl chloride reaction to the preparation of benzo[*b*]thiophenes.[6]

Results and Discussion

Direct Synthesis of Benzo[*b*]thiophenes from Cinnamic Acids, 3-Phenylpropanoic Acids, and Certain 3-Phenyl 1-Substituted 2-Propanones. As described in a preceding paper,[5] cinnamic acid (**3a**) furnished the benzo[*b*]-thiophene **4a** in 69% yield when treated with an excess of thionyl chloride and a catalytic amount of pyridine at 120–125 °C.

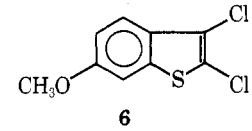


Yield of 4, %

a, X = H; Y = Cl	69
b, X = CH_3; Y = Cl	60.7
c, X = CH_3; Y = OCH_3	40.5
d, X = OCH_3; Y = OCH_3	47.5
e, X = NO_2; Y = OCH_3	46

Similarly *p*-methylcinnamic acid (**3b**) gave benzo[*b*]thiophene **4b** in 60.7% yield and the methyl ester **4c** in 40.5% yield. *p*-Methoxy- (**3d**) and *p*-nitrocinnamic acids (**3e**) furnished benzo[*b*]thiophenes **4d** and **4e** in 47.5 and 46% yield, respectively. The structures of **4a–e** were assigned by spectroscopic data and elemental analyses. No attempt was made to maximize the yields of these products.

Common by-products for the reactions of the acid **3a** to **3d** were α-chlorocinnamic acid derivatives **5**. The reaction of **3e** did not give **5e**, but methyl α,β-dichloro-4-nitrocinnamate and methyl 4-nitrobenzoate as minor products. Another minor product from the reaction of **3d** was the benzo[*b*]thiophene **6** which, isolated in 0.7% yield, showed no carbonyl absorption



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