Unsymmetrically 3,6-Disubstituted *s*-Tetrazines. Synthesis of 3-Aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines and 1,2-Dihydro Derivatives

Kurt Pilgram* and Richard D. Skiles

Biological Sciences Research Center, Shell Development Company, Modesto, California 95352

Received May 10, 1976

A method for the synthesis of 1,2-dihydro-3-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, **8**, from which 3-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, **9**, are obtained by oxidation has been developed. Treatment of a variety of aroylhydrazides, **10**, with perfluorinated aliphatic aldehydes (or their hydrates or hemiacetals) gave 2-(1-hydroxyperfluoroalkyl)aroylhydrazides, **11**, from which perfluorinated aliphatic aldehyde aroylhydrazones, **1**, were produced by dehydration. Treatment of both **11** and **1** with thionyl chloride produced 1-aryl-1-chloro-4-(perfluoroalkyl)azines, **3**, which on treatment with chlorine in carbon tetrachloride or glacial acetic acid afforded 1-aryl-1,4-dichloro-4-(perfluoroalkyl)azines, **7**. Reaction of **7** with hydrazine hydrate, methylhydrazine, and 1,2-dimethylhydrazine gave the title compounds (**8**).

Most of the monocyclic *s*-tetrazines reported in the literature are symmetrically disubstituted compounds.[1,2] Unsymmetrically substituted *s*-tetrazines are considerably more difficult to synthesize, and there are no methods of synthesis that are common for all types. Symmetrical 3,6-diaryl-*s*-tetrazines are available from the reaction of hydrazine with 1,4-diaryl-1,4-dichloroazines, derived from diaroylhydrazines by treatment with phosphorus pentachloride,[3-6] or by chlorination of diarylazines.[7] Here the 1,2-dihydro-*s*-tetrazines are the primary products from which the *s*-tetrazines are obtained by oxidation. We have now examined approaches to the synthesis of 3-aryl-6-(perfluoroalkyl)-*s*-tetrazines, **9**, by way of perfluorinated aliphatic aldehyde aroylhydrazones, **1**, and aromatic aldehyde perfluoroalkanoylhydrazines, **2**.

Results and Discussion

Of the four potential approaches to 1-aryl-1,4-dichloro-4-(perfluoroalkyl)azines, **7**, from acylated aldehyde hydrazones, **1** and **2**, only the first one (path a) has been successful in our hands. The applicability of the other three (path b, c, and d) appears to be limited. For example, attempted chlorination of **1** (X = H; $R_F = CF_3$) in glacial acetic acid failed to give detectable amounts of **4** (X = H; $R_F = CF_3$) after several hours at 35 °C. When **2** (X = H; $R_F = C_3F_7$) was treated with refluxing thionyl chloride containing a small amount of dimethylformamide, the desired chloroazine, **5** (X = H; $R_F = C_3F_7$), was indeed formed in 10–15% yield, but was difficult to separate from by-products. Chlorination of **2** (X = H; $R_F = CF_3$) in glacial acetic acid at 45 °C gave α-chlorobenzaldazine (86%); at 65 °C, the only product isolated was benzal chloride (42%).

In view of the apparent insensitivity of aroylhydrazones, **1**, toward chlorine and the sensitivity toward both chlorine and thionyl chloride of hydrazones **2**, it was surprising that treatment of the **1** compounds with refluxing thionyl chloride gave chloroazines of general structure **3** in good yields and of acceptable purity (80–90%).

For the conversion of **3** into 1,4-dichloroazines, **7**, chlorination in glacial acetic acid or carbon tetrachloride proved satisfactory and gave the desired compounds in good yields (54–100%) and acceptable purity (60–90%) as highly viscous, reactive amber oils. In light of the reactivity of the key intermediates, **7**, no attempt was made to distill them; characterization and determination of purity was by NMR and thin layer chromatography. Depending on the nature of the substituent on the benzene ring, the time required for complete chlorination varied widely both in glacial acetic acid and carbon tetrachloride. Electronegative substituents on phenyl increased the period, e.g., 2–5 h were required for unsubstituted and alkyl-substituted **3**, whereas 12 days were needed for **3** (X = 3-CF_3) at ambient temperature. Progress of chlorinations could be followed by thin layer charomatography.

In one instance, the chlorination procedure led to an unexpected side reaction, 1-chloro-1-(3,5-dimethylphenyl)-

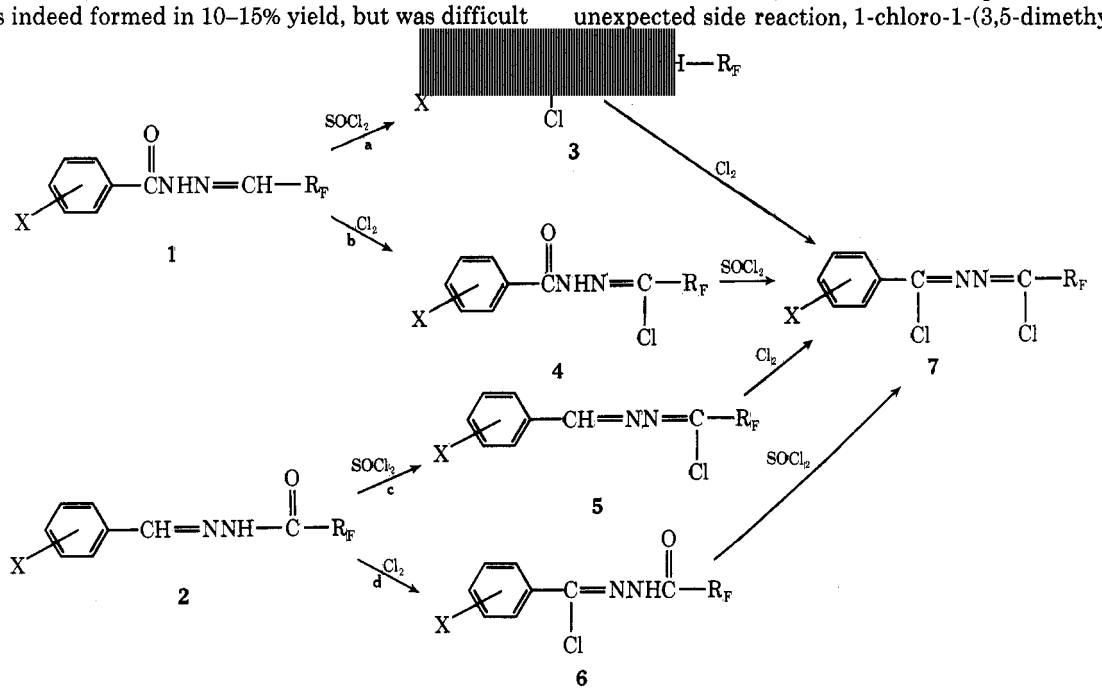


Table I. 1,2-Dihydro-3-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, 8,[a] and 3-Aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, 9[a]

				8				9			
X	R^1	R^2	R_F	% yield	Mp, °C	Molecular formula	Registry no.	% yield	Mp, °C	Molecular formula	Registry no.
H	H	H	CF_3	95	159–161	$C_9H_7F_3N_4$	54820-09-6	81	154–156	$C_9H_5F_3N_4$	56349-37-2
H	H	CH_3	CF_3	33	133–136	$C_{10}H_9F_3N_4$	59872-85-4				
H	CH_3	CH_3	CF_3	32	75–78	$C_{11}H_{11}F_3N_4$	59872-86-5				
H	H	H	C_2F_5	79	161–163	$C_{10}H_7F_5N_4$	54820-10-9	51	117–120	$C_{10}H_5F_5N_4$	56349-40-7
H	H	H	C_3F_7	80	162–164	$C_{11}H_7F_7N_4$	54820-11-0	42	87–89	$C_{11}H_5F_7N_4$	56349-38-3
2-F	H	H	CF_3	33	155–157	$C_9H_6F_4N_4$	59872-87-6	21	68–71	$C_9H_4F_4N_4$	59872-91-2
4-Cl	H	H	CF_3	5	175–177	$C_9H_6ClF_3N_4$	54820-17-6	10	92–94	$C_9H_4ClF_3N_4$[b]	56349-44-1
4-Cl	H	H	C_2F_5	8	157–159	$C_{10}H_6ClF_5N_4$	59872-88-7	90	84–86	$C_{10}H_4ClF_5N_4$	59872-92-3
4-Cl	H	H	C_3F_7	47	140–143	$C_{11}H_8ClF_7N_4$	59872-89-8	92	62–64	$C_{11}H_4ClF_7N_4$	59872-93-4
3,4-Cl_2	H	H	CF_3					4	90–92	$C_9H_3Cl_2F_3N_4$	56349-46-3
3-CF_3	H	H	CF_3	10	132–134	$C_{10}H_6F_6N_4$	54820-13-2				
3-CH_3	H	H	CF_3	73	116–120	$C_{10}H_9F_3N_4$	54820-12-1	30	64–66	$C_{10}H_7F_3N_4$	56349-39-4
4-CH_3	H	H	CF_3	67	188–191	$C_{10}H_9F_3N_4$	54820-15-4	90	152–154	$C_{10}H_7F_3N_4$	56349-42-9
3,4-$(CH_3)_2$	H	H	CF_3	94	149–152	$C_{11}H_{11}F_3N_4$	54820-18-7	28	65–67	$C_{11}H_9F_3N_4$	56349-45-2
3,5-$(CH_3)_2$	H	H	CF_3					22	125–128	$C_{11}H_9F_3N_4$	56349-48-5
3,5-$(CH_3)_2$, 4-Cl	H	H	CF_3	20	197–200	$C_{11}H_{10}ClF_3N_4$[c]	54820-14-3	12	133–135	$C_{11}H_8ClF_3N_4$[d]	56349-41-8
4-$C(CH_3)_3$	H	H	CF_3	81	116–119	$C_{13}H_{15}F_3N_4$	54820-16-5	62	73–75	$C_{13}H_{13}F_3N_4$	56349-43-0
4-NO_2	H	H	CF_3					3	129–131	$C_9H_4F_3N_5O_2$	56349-47-4
3,4-CH=CHCH=CH	H	H	CF_3	56	203–205	$C_{13}H_9F_3N_4$	59872-90-1	27	189–192	$C_{13}H_7F_3N_4$	59872-94-5

[a] All compounds were analyzed for C, H, and N. Except where noted, the results obtained were within ±0.4% of the calculated values. [b] Nitrogen: calcd, 21.5; found, 18.9. [c] Carbon: calcd, 45.4; found 44.4. [d] Carbon: calcd, 45.8; found, 45.2.

4-(trifluoromethyl)azine, **3** [X = 3,5-$(CH_3)_2$; R_F = CF_3], being converted, at 55 °C, rather easily into 1-(4-chloro-3,5-dimethylphenyl)-1,4-dichloro-4-(trifluoromethyl)azine, **7** [X = 4-Cl-3,5-$(CH_3)_2$; R_F = CF_3]. However, chlorination at ambient temperature proceeded smoothly to give **7** [X = 3,5-$(CH_3)_2$; R_F = CF_3] in quantitative yield.

Both 1-chloro- and 1,4-dichloro-1,4-diarylazines have been used as starting materials in heterocyclic synthesis[8-13] and the mechanism of the nucleophilic substitution has been studied in detail.[14] We found that dichloroazines, **7**, also reacted, at 0 °C, in ethanol with hydrazine, methylhydrazine, and 1,2-dimethylhydrazine. Under these conditions, 1,2-dihydro-2-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, **8**, were formed and isolated as tan to light yellow crystalline solids. Yields were generally satisfactory depending on the purity of the precursor 1,4-dichloroazine, **7**. The 1,2-dihydro-*s*-tetrazines so prepared are listed in Table I.

Unambiguous proof of the 1,2-dihydro-*s*-tetrazine structure, **8**, for the reaction products of **7** with hydrazine lies in their conversion by oxidation into the orange to purple-red *s*-tetrazines, **9**. In the present work, oxidation was conveniently and rapidly accomplished by the dropwise addition at 0–25 °C of an aqueous solution of sodium nitrite or ferric chloride to a stirred solution containing **8** in water or ethanol, or alternatively, with hydrogen peroxide in acetic acid. The results of the oxidations are summarized in Table I.

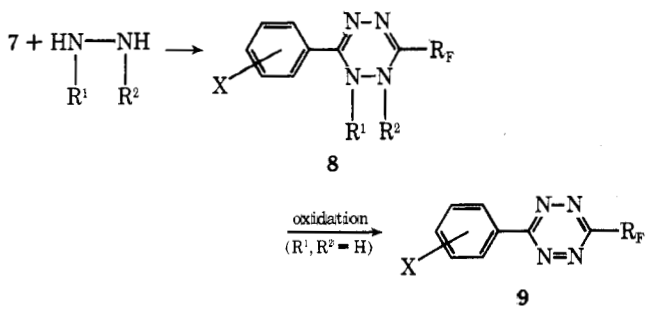


Table II. 2-(1-Hydroxy-2,2,2-trifluoroethyl)-benzoylhydrazides, 11[a]

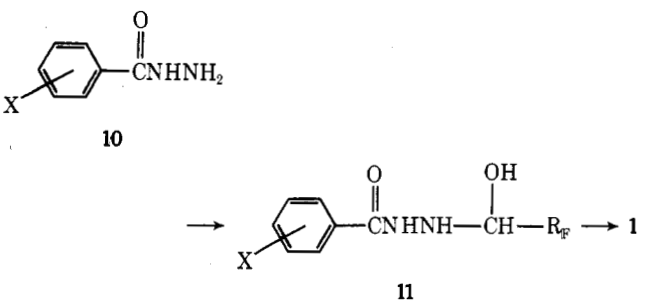
X	% yield	Mp, °C[b]	Molecular formula	Registry no.
H	89	169–171	$C_9H_9F_3N_2O_2$	54820-19-8
2-F	100	125–128	$C_9H_8F_4N_2O_2$	59872-95-6
4-Cl	94	162–164	$C_9H_8ClF_3N_2O_2$	59872-96-7
3-CH_3	85	132–134	$C_{10}H_{11}F_3N_2O_2$	59872-97-8
4-CH_3	76	200–203	$C_{10}H_{11}F_3N_2O_2$	59872-98-9
3,4-$(CH_3)_2$	65	184–187	$C_{11}H_{13}F_3N_2O_2$	59872-99-0
3,5-$(CH_3)_2$	89	185–188	$C_{11}H_{13}F_3N_2O_2$	59888-80-1
4-$C(CH_3)_3$	95	162–165	$C_{13}H_{17}F_3N_2O_2$	59873-00-6

[a] Satisfactory analytical data were obtained for all compounds listed in this table (±0.4% for C, H, and N). [b] With decomposition (dehydration).

Experimental Section

Materials. Trifluoroacetaldehyde hydrate, pentafluoropropionaldehyde methyl hemiacetal, heptafluorobutyraldehyde ethyl hemiacetal, and trifluoroacetyl chloride were obtained commercially.

Perfluorinated aliphatic aldehyde aroylhydrazones, **1**, were prepared by the following route. In this synthesis, a hydrazide, **10** (prepared by literature procedures), was allowed to react with a perfluorinated aldehyde, R_F-CHO (or its hydrate or hemiacetal), to give **11**



from which **1** was obtained by dehydration. The products, **11** and **1**, so obtained are listed in Tables II and III, respectively.

Table III. Perfluorinated Aliphatic Aldehyde Aroylhydrazones, 1[a]

X	R_F	% yield	Mp, °C	Molecular formula	Registry no.
H	CF_3	67	191–193	$C_9H_7F_3N_2O$	54820-20-1
H	C_2F_5	81	150–152	$C_{10}H_7F_5N_2O$	54820-23-4
H	C_3F_7	80	118–120	$C_{11}H_7F_7N_2O$	583-14-2
2-F	CF_3	100	170–172	$C_9H_6F_4N_2O$	59873-01-7
4-Cl	CF_3	80	203–205	$C_9H_6ClF_3N_2O$	59873-02-8
4-Cl	C_2F_5	88	171–173	$C_{10}H_6ClF_5N_2O$	59873-03-9
4-Cl	C_3F_7	83	138–140	$C_{11}H_6ClF_7N_2O$	59873-04-0
3-CH_3	CF_3	100	151–153	$C_{10}H_9F_3N_2O$	59873-05-1
3,5-$(CH_3)_2$	CF_3	61	185–188	$C_{11}H_{11}F_3N_2O$	59873-06-2
4-$C(CH_3)_3$	CF_3	45	208–210	$C_{13}H_{15}F_3N_2O$	59873-07-3
2-Cl	CF_3	82	190–192	$C_9H_6ClF_3N_2O$	59873-08-4
3,4-Cl_2	CF_3	97	168–170	$C_9H_5Cl_2F_3N_2O$	59872-47-8
4-NO_2	CF_3	86	240–242	$C_9H_6F_3N_3O_3$	59872-48-9
3-CF_3	CF_3	93	138–141	$C_{10}H_6F_6N_2O$	59872-49-0
3,5-$(CF_3)_2$	CF_3	56	204–207	$C_{11}H_5F_9N_2O$	59872-50-3
3,4-CH=CHCH=CH	CF_3	100	208–210	$C_{13}H_9F_3N_2O$	59872-51-4

[a] Satisfactory analytical data were obtained for all compounds listed in this table (±0.4% for C, H, and N).

Benzaldehyde Trifluoroacetylhydrazone, 2 (X = H; R_F = CF_3). This compound was prepared in 20% yield from benzalhydrazone and trifluoroacetyl chloride in tetrahydrofuran (−20 °C) containing 1 molar equiv of triethylamine, mp 132–135 °C.

Anal. Calcd for $C_9H_7F_3N_2O$: C, 50.8; H, 3.2; N, 13.0. Found: C, 50.5; H, 3.4; N, 13.1.

Benzaldehyde Heptafluorobutyrylhydrazone, 2 (X = H; R_F = C_3F_7). This compound was prepared in 96% yield from heptafluorobutyric acid hydrazide (mp 75–77 °C) and benzaldehyde in ethanol containing several drops of concentrated hydrochloric acid and had mp 95–98 °C.

Anal. Calcd for $C_{11}H_7F_7N_2O$: C, 41.8; H, 2.2; N, 8.9. Found: C, 41.9; H, 2.2; N, 8.7.

The general procedures used for the steps 11 → 1 → 3 → 7 → 8 → 9 are illustrated using two examples.

1,2-Dihydro-3-phenyl-6-(trifluoromethyl)-1,2,4,5-tetrazine, 8 (R^1, R^2, X = H; R_F = CF_3). A. 2-(1-Hydroxy-2,2,2-trifluoroethyl)benzhydrazide, 11 (X = H; R_F = CF_3). To a warm (55 °C) solution containing 110 g (0.81 mol) of benzhydrazide in 600 ml of water was added with stirring 99.6 g (0.86 mol) of trifluoroacetaldehyde hydrate, causing a white solid to precipitate almost instantaneously. The stirred reaction mixture then was heated to 80–90 °C for 1 h, cooled to room temperature, and filtered to give 128 g of colorless solid. Concentration of the filtrate to dryness gave 30.6 g of additional solid. The total product, 169.4 g (89%), was a colorless solid: ir (KBr) 3100 (NH), 1650 (C=O), and 1150–1200 cm^{-1} (CF_3).

B. Trifluoroacetaldehyde Benzoylhydrazone, 1 (X = H; R_F = CF_3). A slurry of 168.6 g (0.72 mol) of 11 (X = H; R_F = CF_3) in 600 ml of thionyl chloride was stirred at room temperature until evolution of gases (HCl + SO_2) has ceased (about 0.5 h). The reaction mixture was concentrated under reduced pressure and the residual solid was recrystallized from methanol to give 104.5 g (67%) of colorless, crystalline solid: ir (KBr) 3370 and 3140 (NH), 1640 (C=N, C=O), and 1230 cm^{-1} (CF_3).

C. 1-Chloro-1-phenyl-4-(trifluoromethyl)azine, 3 (X = H; R_F = CF_3). A solution containing 120 g (0.52 mol) of 1 (X = H; R_F = CF_3) in 250 ml of thionyl chloride was refluxed for 18 h and concentrated under reduced pressure. The residual amber liquid was distilled to give 99.5 g (83%) of amber liquid: bp 70–72 °C (0.5 mm); ir, no apparent C=O or NH; 1000 (C=) and 1180 cm^{-1} (CF_3); NMR ($CDCl_3$) 7.5 (4, CH=) and 8.0 ppm (2, CH=); mass spectrum (70 eV) *m/e* 234 (M^+), 199 (M^+ − Cl, base peak), 165 (M^+ − CF_3), 138 [C_6H_5 − C(Cl)N^+], 129 (M^+ − CF_3 − HCl), 104, 103 ($C_6H_5C{\equiv}N^+$), 89 ($C_6H_5C^+$), 69 (CF_3^+).

Anal. Calcd for $C_9H_6ClF_3N_2$: Cl, 15.2. Found: Cl, 15.4.

D. 1,4-Dichloro-1-phenyl-4-(trifluoromethyl)azine, 7 (X = H; R_F = CF_3). Chlorine, 51.2 g (0.72 mol), was passed gradually over a period of 5 h into a solution of 169 g (0.72 mol) of 3 (X = H; R_F = CF_3) in 500 ml of glacial acetic acid. The temperature of the mixture rose to 50 °C. Concentration of the reaction mixture gave an oil that was dissolved in methylene chloride and washed with cold aqueous sodium bicarbonate and then with water. After drying, the solution was concentrated and the residual liquid was distilled to give 135 g (70%) of light red liquid: bp 66–68 °C (0.05 mm); ir (CH_2Cl_2) 1640 (C=N), 1600, 1590, 1500, and 1460 (aromatic), 1220 (CF_3), and 760 cm^{-1} (C–Cl); NMR ($CDCl_3$) 7.4–8.2 ppm (CH=); mass spectrum (70 eV) *m/e* 268 (M^+), 233 (M^+ − Cl), 197 (M^+ − 2HCl), 138 [C_6H_5 − C(Cl)N^+], 103 ($C_6H_5C{\equiv}N^+$, base peak), 89 ($C_6H_5C^+$), 69 (CF_3^+), 36 (HCl^+), 20 (HF^+).

Anal. Calcd for $C_9H_5Cl_2F_3N_2$: Cl, 25.4. Found: Cl, 24.8.

When this reaction was carried out in carbon tetrachloride, at 25 °C and 60 h, saturated with chlorine, the yield was 91%.

E. Preparation of 8 (R^1, R^2, X = H; R_F = CF_3). To a solution of 13.5 g (0.05 mol) of 7 (X = H; R_F = CF_3) in 100 ml of ethanol was added at 0–5 °C with stirring 5.1 g (0.15 mol) of 95% hydrazine. The mixture was stirred at room temperature for 3 h, then concentrated under reduced pressure, and the residue was washed with water and filtered. Recrystallization of the residual solid from benzene gave 10.5 g (95%) of yellow crystalline solid; ir (KBr) 3300 (NH), 1700, 1650, and 1585 (C=), and 1150 cm^{-1} (CF_3); NMR (Me_2SO-d_6) 7.2–7.9 (5, m, CH=) and 9.27 and 9.40 ppm (2, NH); mass spectrum (70 eV) *m/e* 228 (M^+).

3-Phenyl-6-(trifluoromethyl)-1,2,4,5-tetrazine, 9 (X = H; R_F = CF_3). A solution of 90 g (0.56 mol) of ferric chloride in 250 ml of water was added to a warm (40 °C) solution of 68 g (0.3 mol) of 8 (R^1, R^2, X = H; R_F = CF_3) in 350 ml of ethanol and 175 ml of water. The mixture was briefly heated to 80 °C, then cooled and filtered. Recrystallization of the filter cake from hexane–ether (1:1) gave 54 g (81%) of red crystalline solid: ir (CH_2Cl_2) 1600, 1450 (C=), 1320, 1200, 1170, and 1140 cm^{-1} (CF_3); NMR ($CDCl_3$) 7.5–7.85 (3, CH=) and 8.8–9.3 ppm (2, CH=).

1,2-Dihydro-3-(2-naphthyl)-6-(trifluoromethyl)-1,2,4,5-tetrazine, 8 (R^1, R^2 = H; X = 3,4-(CH=CHCH=CH); R_F = CF_3). A. Trifluoroacetaldehyde 2-Naphthoylhydrazone, 1 (X = 3,4-(CH=CHCH=CH); R_F = CF_3). A mixture containing 93 g (0.5 mol) of 2-naphthoic acid hydrazide, 116 g (1.0 mol) of trifluoroacetaldehyde hydrate, and 5 drops of concentrated sulfuric acid in 400 ml of ethanol was refluxed for 20 h. The solvent was removed and the residue was washed well with ether, filtered, and dried to give 134 g (100%) of a colorless solid: ir (KBr) 3240 (NH) and 1660 cm^{-1} (C=O); NMR (Me_2SO-d_6) 7.5–8.5 (8, CH=) and 12.55 ppm (1, NH).

B. 1-Chloro-1-(2-naphthyl)-4-(trifluoromethyl)azine, 3 (X = 3,4-(CH=CHCH=CH); R_F = CF_3). A solution of 133 g (0.5 mol) of the hydrazone prepared under A and 10 drops of dimethylformamide in 500 g of thionyl chloride was refluxed for 5 h, and then concentrated under reduced pressure. The residue was dissolved in ether, washed with water, dried, and concentrated. The residual yellow oil, 144 g (100%), crystallized on standing.

Anal. Calcd for $C_{13}H_8ClF_3N_2$: Cl, 12.5. Found: Cl, 12.1.

C. 1,4-Dichloro-1-(2-naphthyl)-4-(trifluoromethyl)azine, 7 (X = 3,4-(CH=CHCH=CH); R_F = CF_3). Chlorine, 40 g (0.56 mol), was introduced into a stirred solution containing 142.5 g (0.50 mol) of the chloroazine prepared under B in 300 ml of carbon tetrachloride. After 2 h, the solvent and excess of chlorine were removed under reduced pressure leaving 159 g (99%) of yellow syrup.

Anal. Calcd for $C_{13}H_7Cl_2F_3N_2$: Cl, 22.3. Found: Cl, 23.2.

D. Preparation of 8 (R^1, R^2 = H; X = 3,4-(CH=CHCH=CH); X = CF_3). To a stirred and cooled (0 °C) solution of 159 g (0.5 mol) of the dichloroazine prepared under C in 300 ml of ethanol was added dropwise (about 20 min) 51 g (1.5 mol) of 95% hydrazine. The reaction

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.

References and Notes

(1) P. F. Wiley, "The Chemistry of Heterocyclic Compounds, the 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines", A. Weissberger, Ed., Interscience, New York, N.Y., 1956, Chapter V.
(2) V. P. Wystrach, "Heterocyclic Compounds", Vol. 8, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1967, Chapter II.
(3) R. Stolle, *J. Prakt. Chem.*, **68**, 464 (1903); **73**, 277 (1906).
(4) R. Stolle and Thoma, *J. Prakt. Chem.*, **73**, 288 (1906).
(5) R. Stolle and A. Weindel, *J. Prakt. Chem.*, **74**, 550 (1906).
(6) A. Bambach and R. Stolle, *J. Prakt. Chem.*, **74**, 13 (1906).
(7) R. Stolle, *J. Prakt. Chem.*, **85**, 386 (1912).
(8) W. T. Flowers, D. R. Taylor, A. E. Tipping, and C. N. Wright, *J. Chem. Soc. C*, 1986 (1971).
(9) F. Helwerth and R. Stolle, *Ber.*, **47**, 1132 (1914).
(10) R. Stolle and A. Netz, *Ber.*, **55**, 2197 (1922).
(11) P. G. Ugrymov, *J. Gen. Chem. USSR (Engl. Transl.)*, **29**, 4050 (1959).
(12) R. Fusco and S. Rossi, *Ann. Chim. (Rome)*, **50**, 277 (1960).
(13) J. K. O'Halloran and F. L. Scott, *J. Chem. Soc. D*, 426 (1971).
(14) P. A. Cashell, A. F. Hegartz, and F. L. Scott, *Tetrahedron Lett.*, 4767 (1971).

Smiles Rearrangement of 2-Tetrazolylthio-3-aminopyridines

Henry W. Altland

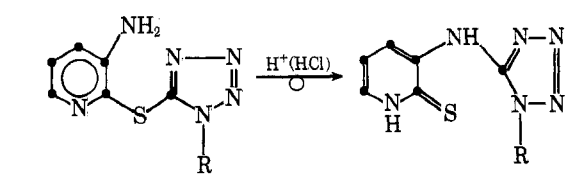
Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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.

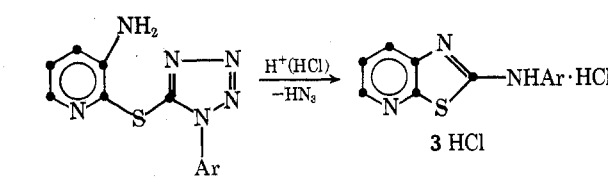
The Smiles rearrangement is an intramolecular nucleophilic aromatic substitution.[1,2] The scope of this reaction increases as more papers describing this rearrangement of a diversity of molecular systems are being published. Smiles recognized that certain diaryl sulfides undergo an intramolecular nucleophilic 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-