[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

The Chemistry of Sulfur Tetrafluoride. IX. Reaction with Amino Acids in Hydrogen Fluoride[1]

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Sulfur tetrafluoride converts the carboxyl group in amino acids to a trifluoromethyl group when the reaction is carried out in hydrogen fluoride. When an optically active amino acid is used, optical activity is retained in the resulting fluoro amine.

Sulfur tetrafluoride is a versatile reagent for converting carboxyl groups to trifluoromethyl groups as reported from this laboratory.[2]

$$RCOOH + 2SF_4 \longrightarrow RCF_3 + 2SOF_2 + HF$$

Carrying out the reaction on amino acids is a special problem and this article summarizes our results with such compounds.

Though the direct action of sulfur tetrafluoride on amino acids containing hydrogen-bearing amino groups usually leads to intractable products, the conversion of the carboxyl group to trifluoromethyl can be carried out on many aliphatic amino acids in modest yields if the reaction is performed in hydrogen fluoride, which serves to protect the amino group. Moreover, when an optically active amino acid is used, optical activity is retained in the resulting amine. Although many fluoro amines have been reported,[3] the sulfur tetrafluoride reaction provides a useful supplement to previous methods.

The amines prepared by this method are listed in Table I. In general, a standard set of conditions was used as described in the Experimental without exploration of variables to give optimum yields. Structural factors are important in determining yields. An amino acid capable of forming a lactam (4-aminobutyric acid) gives a low yield. If diketopiperazine formation is hindered or impossible, yield is enhanced. Thus, *N*-dodecylalanine gave a 61% yield compared to 29% for alanine; and, in the series of carboxypiperidines, the 3- and 4-carboxypiperidines gave higher yields than the 2-derivative. Sensitive functional groups may prevent a successful reaction. Thus, methionine gave only a 1.5% yield; and the desired amines were not isolated from serine, cystine, tyrosine, tryptophane, and histidine. Direct action of sulfur tetrafluoride on nicotinic acid gave nicotinyl fluoride and no 3-(trifluoromethyl)pyridine, but when the reaction was run in hydrogen fluoride, a 25% yield of 3-(trifluoromethyl)pyridine was obtained. Yields from other carboxy derivatives of aromatic nitrogen heterocycles ranged to 80%.

The retention of optical activity during the reaction is illustrated by the products from L-leucine and L-glutamic acid. The optical rotations of the resulting L-3-methyl-1-(trifluoromethyl)-butylamine and L-4,4,4-trifluoro-1-(trifluoromethyl)-butylamine were $[\alpha]^{23}D$ −38.5° and $[\alpha]^{22}D$ −36.9°, respectively, measured on the pure amines in a 0.4-dm. tube.

The inductive effect of the trifluoromethyl group in decreasing the basicity of amines has previously been noted by Henne and Stewart[4] for $CF_3CH_2NH_2$ and $CF_3CH_2CH_2NH_2$. An extended illustration of this effect appears in the approximate pK_a data in Table I for the amines $CF_3(CH_2)_nNH_2$ where n is 1,2, and 3 and for the 2-, 3-, and 4-trifluoromethylpiperidines. The basicity decreases with the nearness of the trifluoromethyl group to the amino group. The trifluoromethyl derivatives of pyridine and quinoline are extremely weak bases, but unstable hydrochlorides can be made by passing hydrogen chloride into ether solutions of the heterocycles.

As a related effect, the trifluoromethyl group can be expected to decrease the hydrogen bonding associated with the amino group. This will be reflected in the boiling point. Table III illustrates a series of 1-trifluoromethyl amines in which the increase in boiling point of the lower members due to increased molecular weight is overcome in ascending the series so that the higher members have slightly lower boiling points than the corresponding unfluorinated amines.

Of the twenty-four fluoro amines recorded here, seven have been reported previously. 2,2,2-Trifluoromethylamine has been made by the ammonolysis of 1-bromo-2,2,2-trifluoroethane and other routes,[3] 3,3,3-trifluoropropylamine from 4,4,4-trifluorobutyramide and 4,4,4-trifluorobutyrylazide,[4] and 1-(trifluoromethyl)ethylamine by the reduc-

(1) Paper VIII, W. C. Smith, *J. Am. Chem. Soc.*, 82, 6176 (1960).

(2) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, 82, 543 (1960); W. C. Smith, U. S. Patent 2,859,245 (1958).

(3) A. M. Lovelace, D. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Corp., New York, 1958, pp. 282–306.

(4) A. L. Henne and J. J. Stewart, *J. Am. Chem. Soc.*, 77, 1901 (1955).

TABLE I

FLUORO AMINES

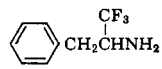
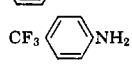
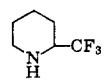
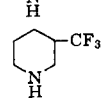
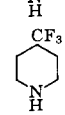
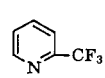
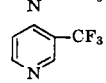
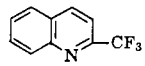
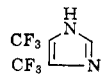
Compound	Structure	Starting Amino Acid	Yield, %	B.P.	$n^{25}D$	pK_a[a]
1. 2,2,2-Trifluoroethylamine	$CF_3CH_2NH_2$	Glycine	24	36	1.3004	5.6
2. 3,3,3-Trifluoropropylamine	$CF_3(CH_2)_2NH_2$	β-Alanine	41	67.5–68	1.3270	8.6
3. 4,4,4-Trifluorobutylamine	$CF_3(CH_2)_3NH_2$	4-Aminobutyric acid	7.1	90–91	1.3452	9.6
4. DL-1-(Trifluoromethyl)ethylamine	$CH_3\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH_2$	DL-Alanine	29	46–47	1.3180	5.8
5. DL-1-(Trifluoromethyl)propylamine	$CH_3CH_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH_2$	DL-2-Aminobutyric acid	3.5	65–66		5.7
6. DL-1-(Trifluoromethyl)butylamine	$CH_3(CH_2)_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH_2$	DL-Norvaline	2.5	87–88	1.3568	5.7
7. DL-1-(Trifluoromethyl)pentylamine	$CH_3(CH_2)_3\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH_2$	DL-Norleucine	14	113–116	1.3635	5.7
8. DL-1-(Trifluoromethyl)heptylamine	$CH_3(CH_2)_5\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH_2$	DL-2-Aminooctanoic acid	39	158–160	1.3825	
9. 2,2,2-Trifluoro-1,1-dimethylethylamine	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{\overset{\displaystyle CF_3}{\overset{\vert}{C}}}}NH_2$	2-Methylalanine	35	54	1.3305	5.8
10. DL-2-Methyl-1-(trifluoromethyl)propylamine	$CH_3CH(CF_3)CHNH_2$	DL-Valine	4.2	83–84	1.3540	5.6
11. L-3-Methyl-1-(trifluoromethyl)butylamine	$CH_3CH(CH_3)CH_2CHNH_2$	L-Leucine	22	103–104	1.3610	5.6
12. L-4,4,4-Trifluoro-1-(trifluoromethyl)butylamine	$CF_3(CH_2)_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH_2$	L-Glutamic acid	12[b]	106	1.3222	4.7
13. DL-3-(Methylthio)-1-(trifluoromethyl)propylamine	$CH_3S(CH_2)_2\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH_2$	DL-Methionine	1.5	160–162	1.4260	4.8
14. DL-*N*-[1-(Trifluoromethyl)ethyl]-dodecylamine	$CH_3\underset{\displaystyle CF_3}{\underset{\vert}{C}}HNH(CH_2)_{11}CH_3$	*N*-Dodecyl-DL-alanine	61	74–76/0.18 mm.	1.4119	
15. DL-α-(Trifluoromethyl)phenethylamine		DL-Phenylalanine	3.6	53–55/1 mm.	1.4613	
16. *p*-Aminobenzotrifluoride		*p*-Aminobenzoic acid	37	85/14 mm.		
17. DL-2-(Trifluoromethyl)piperidine		Sodium DL-pipecolate	9.6	122–124	1.3905	6.4
18. DL-3-(Trifluoromethyl)piperidine		Sodium DL-nipecotate	40	128–130	1.3910	8.7
19. DL-4-(Trifluoromethyl)piperidine		Sodium isonipecotate	34	133	1.3920	9.4
20. 2-(Trifluoromethyl)pyridine		Picolinic acid	53	139–140	1.4166	
21. 3-(Trifluoromethyl)pyridine		Nicotinic acid	25	113–115	1.4150	
22. 4-(Trifluoromethyl)pyridine		Isonicotinic acid	57	108–110	1.4155	

TABLE I (*Continued*)

Compound	Structure	Starting Amino Acid	Yield, %	B.P.	$n^{25}D$	pK_a[a]
23. 2-(Trifluoromethyl)quinoline		Quinaldic acid	72	233 M.P. 61.5–62.5		
24. 4,5-Bis(trifluoromethyl)imidazole		4,5-Imidazoledicarboxylic acid	80	M.p. 167.5–168		

[a] pH at half-neutralization in ca. 0.02 *M* solution in H_2O, glass electrode. Value for NH_3, 9.2; *n*-butylamine, 10.6. [b] Best result. Difficulty has been encountered in repeating this experiment. The amine was purified by gas chromatography over Dow Corning silicone oil No. 703 on firebrick.

TABLE II

ANALYTICAL DATA FOR COMPOUNDS OF TABLE I

Compound	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Fluorine, % Calcd.	Fluorine, % Found
3	$C_4H_8F_3N$	37.80	38.35	6.35	6.56	44.85	45.09
5	$(C_4H_8F_3N\cdot HCl)$	29.40	29.86	5.55	5.62	34.88	35.00
6	$C_5H_{10}F_3N$	42.56	43.46	7.15	7.60	40.40	39.98
7	$C_6H_{12}F_3N$	46.43	46.88	7.80	8.14	36.73	36.94
8	$C_8H_{16}F_3N$	52.44	52.99	8.80	8.85	31.11	31.73
9	$C_4H_8F_3N$	37.80	38.57	6.35	6.23	44.85	45.04
10	$C_5H_{10}F_3N$	42.47	43.07	7.13	7.42	40.32	39.46
11	$C_6H_{12}F_3N$	46.43	46.85	7.80	8.24	36.72	36.62
12	$C_5H_7F_6N$[a]	30.79	31.30	3.62	4.21	58.43	57.88
13	$C_5H_{10}F_3NS$	34.67	34.76	5.82	5.22	32.92	32.69
14	$C_{15}H_{30}F_3N$	64.01	65.10	10.75	10.78	20.25	20.12
15	$C_9H_{19}F_3N$	57.12	57.60	5.33	5.74	30.12	30.15
16	$C_7H_6F_3N$	52.2	52.1	3.7	3.9	35.4	35.6
17	$C_6H_{10}F_3N$	47.04	48.23	6.58	6.75	37.22	37.01
18	$C_6H_{10}F_3N$	47.04	47.46	6.58	6.63	37.22	37.64
19	$C_8H_{10}F_3N$	47.04	47.70	6.58	6.29	37.22	37.52
20	$C_6H_4F_3N$	48.99	49.70	2.74	2.84	38.75	39.10
21	$C_6H_4F_3N$	48.99	49.53	2.74	2.81	38.75	38.99
22	$C_6H_4F_3N$	48.99	49.45	2.74	3.14	38.75	39.02
23	$C_{10}H_6F_3N$	60.90	61.31	3.07	3.08	28.90	28.95
24	$C_5H_2F_6N_2$	29.43	29.70	0.49	1.30	55.86	55.79

[a] Nitrogen, %: Calcd., 7.18. Found, 7.04.

TABLE III

COMPARISON OF BOILING POINTS

n	$CH_3(CH_2)_nCH(CH_3)NH_2$	$CH_3(CH_2)_nCH(CF_3)NH_2$
0	33	47
1	63	65
2	91	88
3	118	115
5	164	160

tion of 1,1,1-trifluoroacetone oxime.[5] α-(Trifluoromethyl)phenethylamine has been prepared by reductive amination of trifluoromethyl benzyl ketone.[6] *p*-Aminobenzotrifluoride is a commercial chemical. 2-(Trifluoromethyl)pyridine has been synthesized by passing trifluoroacetonitrile and butadiene through a hot tube.[7] The infrared spectrum obtained here agrees with that reported. 2-(Trifluoromethyl)quinoline is said to be formed by the fluorination of 2-[tri(chloro or bromo)methyl]quinoline with antimony trifluoride,[8] but the product was not characterized.

EXPERIMENTAL

Materials. The sulfur tetrafluoride was made by the procedure of Tullock[9] and supplied by the Organic Chemicals Department, E. I. du Pont de Nemours and Co. Except for the following, the amino acids used were commercial research chemicals.

Picolinic, nicotinic, and isonicotinic acids were converted into the sodium salts of pipecolic, nipecotic, and isonipecotic acids by dissolving 100 g. (0.81 mole) of the unsaturated acid in 300 ml. of water containing 33 g. (0.82 mole) of sodium hydroxide and charging the solution and 3 g. of ruthenium-on-carbon catalyst into a 1-l. bomb lined with stainless steel. The solution was then hydrogenated at 120° for 9 hr., filtered, and evaporated to dryness. The sodium salt obtained was dried in a vacuum oven at 90° for 16 hr.

N-Dodecyl-DL-alanine was prepared by heating a mixture of 95 g. (0.51 mole) of dodecylamine and 18.5 g. (0.17 mole) of 2-chloropropionic acid at 100° for 15 hr. The product was washed at 25° with ethanol. There remained 19 g. (43% yield) of *N*-dodecyl-DL-alanine. After recrystallization from acetic acid–water in 96% return, it melted at 210–213°.

Anal. Calcd. for $C_{15}H_{31}NO_2$: N, 5.44. Found: N, 5.45.

Preparation of the compound, without characterization, by another route has been described.[10]

Reaction conditions. The general procedure was to heat at 120° for 8 hr. a mixture of 0.4 equivalent, based on carboxyl, of the amino acid, 50 g. (2.5 moles) of hydrogen fluoride, and 100 g. (0.93 mole) of sulfur tetrafluoride in a 400-ml. shaker tube lined with stainless steel. Good agitation should be used. The stainless steel was attacked to a small extent. A Hastelloy lining appears less subject to attack except in the case of the pyridinic compounds. Conditions for optimum yields have not been studied. However, in the case of *p*-aminobenzoic acid, a greater quantity of hydrogen fluoride must be used to obtain a reasonable yield. We are indebted to Dr. V. Weinmayr, of du Pont's Jackson Laboratory, for this experiment. Fourteen grams (0.1 mole) of *p*-aminobenzoic acid, 100 g. (5 moles) of hydrogen fluoride, and 30 g. (0.28 mole) of sulfur tetrafluoride were heated to 125° during 4 hr. and maintained there for 6 hr. to obtain a 37% yield of *p*-aminobenzotrifluoride. With 2-

(5) J. B. Dickey, E. B. Towne, M. S. Bloom, G. J. Taylor, D. J. Wallace, J. Sagal, Jr., M. A. McCall, and D. G. Hedberg, *Ind. Eng. Chem.*, **48**, 209 (1956); J. B. Dickey and E. B. Towne, U. S. Patent **2,537,976** (1951).

(6) W. R. Nes and A. Burger, *J. Am. Chem. Soc.*, **72**, 5409 (1950).

(7) J. M. S. Jarvie, W. E. Fitzgerald, and G. J. Janz, *J. Am. Chem. Soc.*, **78**, 978 (1956); J. M. S. Jarvie and G. J. Janz, *J. Phys. Chem.*, **60**, 1430 (1956); G. J. Jans and M. A. De Crescente, *J. Org. Chem.*, **23**, 765 (1958).

(8) J. B. Dickey and J. G. McNally, U. S. Patent **2,432,393** (1947) and **2,442,345** (1948).

(9) C. W. Tullock, F. S. Fawcett, W. C. Smith, and D. D. Coffman, *J. Am. Chem. Soc.*, **82**, 539 (1960); C. W. Tullock, U. S. Patent **2,992,073** (1961).

(10) W. L. Alderson, Jr., and P. R. Austin, U. S. Patent **2,328,940** (1943).

aminobutyric acid, additional hydrogen fluoride did not raise the low yield.

In the absence of hydrogen fluoride, sulfur tetrafluoride converts nicotinic acid to nicotinyl fluoride. Nicotinic acid (20 g. 0.16 mole), sulfur tetrafluoride (40 g. 0.37 mole), and 0.2 g. of water were heated for 4 hr. at 100° and 6 hr. at 120°. Distillation of the product gave a 50% yield of nicotinyl fluoride, b.p. 50–52°/6 mm.[11] The compound is quickly hydrolyzed by water.

Isolation procedures. Except for the picolines, the reaction products were poured into a polyethylene dish and heated on a steam bath to expel hydrogen fluoride. From this point the procedure may vary. The residue, especially if tarry, may be transferred to a steam-distillation apparatus, made strongly alkaline with sodium hydroxide solution, and steam distilled. The higher, sparingly soluble amines may be collected from the distillate with ether and dried and distilled in the usual manner. For the lower, water-soluble amines it is best to make the steam distillate acid with hydrochloric acid and evaporate the solution to dryness to obtain the amine hydrochloride which may, however, contain ammonium chloride as a contaminant. The amine may then be liberated from the hydrochloride with 40% potassium hydroxide solution, separated, dried over sodium hydroxide, and distilled.

In the case of the products from simple, aliphatic amino acids, the residue remaining after the evaporation of hydrogen fluoride may be stirred with water and filtered to separate insoluble materials from the amine hydrofluoride. The filtrate may then be evaporated to obtain the solid amine hydrofluoride from which tarry contaminants can be removed by washing with acetone. The amine can then be liberated with 40% potassium hydroxide and collected. However, precipitated heavy metal hydroxides formed from salts produced by attack on the stainless-steel reaction tube may cause minor difficulties here.

The trifluoromethylpicolines are volatile and such weak bases that evaporation of the reaction mixture, unless carefully done, will result in loss of the free picoline. Hence, the reaction mixture was diluted with 75 ml. of water and made basic with 33% sodium hydroxide while being cooled with ice. The mixture was then steam distilled. The oil was separated and the aqueous layer was extracted once with ether. The combined oil and ether extract were dried and distilled.

The product obtained from quinaldic acid was warmed to expel most of the hydrogen fluoride, and the residue was stirred with water. The crystalline 2-(trifluoromethyl)quinoline was filtered off, washed with water, air-dried, and recrystallized from hexane. The product from 4,5-imidazoledicarboxylic acid was treated similarly. The air-dried 4,5-bis(trifluoromethyl)imidazole was dissolved in ether and decolorized. Benzene was added and the ether was boiled away until the product crystallized out. The compound is soluble in aqueous sodium hydroxide.

WILMINGTON, DEL.

(11) Results supplied through the courtesy of Dr. R. J. Harder.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, MIDWEST RESEARCH INSTITUTE]

Synthesis of *t*-Butylsilicon Compounds by the Wurtz-Fittig Reaction[1]

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The Wurtz-Fittig reaction of *t*-butyl chloride with tetramethoxysilane, tetraethoxysilane, tetraisopropoxysilane, and phenyltrimethoxysilane gave *t*-butyltrimethoxysilane, *t*-butyltriethoxysilane, *t*-butyltriisopropoxysilane, and *t*-butyldimethoxyphenylsilane in average yields of 40, 40, 13, and 35%, respectively. Reactions of chlorodiethoxysilane and triethoxysilane with *t*-butyl chloride and molten sodium gave *t*-butyltriethoxysilane instead of *t*-butyldiethoxysilane. Reactions attempted with methyltrichlorosilane, chlorodiethoxymethylsilane, chlorodiisopropoxymethylsilane, and silicon tetrachloride did not yield any *t*-butylated products. During all the reactions, some of the *t*-butyl chloride was converted to volatile off-gases. In nearly all cases these off-gases were composed mainly of an equal molar mixture of isobutane and isobutylene. The infrared spectra of *t*-butyltrimethoxysilane and *i*-butyltrimethoxysilane were determined. It was found that the number and intensity of the absorption bands in these compounds which are due to the *t*-butyl group and the *i*-butyl group are exactly opposite to the spectral correlations for ordinary aliphatic hydrocarbons which contain these groups.

t-Butylsilicon compounds have been prepared by treating various chlorosilanes with *t*-butyllithium[3] and *t*-butylmagnesium chloride.[4] During a study of the Wurtz-Fittig reaction in the preparation of organosubstituted silanes, Emblem and co-workers[5,6] were unable to obtain a *t*-butylsilicon product from the reaction of *t*-butyl bromide, silicon tetrachloride, and sodium.

This paper reports the preparation of several *t*-butylsilicon compounds by the Wurtz-Fittig reaction of certain silicon compounds with *t*-butyl chloride and sodium. The results of the study are summarized in Table I.

Production of t-butylsilicon compounds by the Wurtz-Fittig reaction. The reaction of tetraethoxysilane and *t*-butyl chloride with molten sodium gave *t*-butyltriethoxysilane. A vapor phase chromatogram and an infrared spectrum of the reaction product were identical with those of an authentic sample of *t*-butyltriethoxysilane. The *t*-butyltri-

(1) This research was sponsored by the Research and Development Department of the Ethyl Corp., Baton Rouge, La.

(2) Present address: Corn Industries Research Foundation, Washington, D. C.

(3) L. J. Tyler, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 2876 (1948).

(4) M. C. Harvey, W. H. Nebergall, and J. S. Peake, *J. Am. Chem. Soc.*, **79**, 2762 (1957).

(5) E. A. Bassett, H. G. Emblem, M. Frankel, and D. Ridge, *J. Soc. Chem. Ind.*, **67**, 177 (1948).

(6) H. G. Emblem, D. Ridge, and M. Todd, *Chem. and Ind.* (London), 905 (1955).