Journal of Fluorine Chemistry, 12 (1978) 293-305

Received: April 4, 1978

SYNTHESIS OF SOME TRIFLUOROETHYL-SUBSTITUTED DERIVATIVES OF ANILINE

EUGENE R. BISSELL AND ROSALIND W. SWANSIGER

Lawrence Livermore Laboratory, University of California
Livermore, California 94550 USA

SUMMARY

A new procedure is presented for the preparation of N-trifluoroethylanilines by reaction of the appropriate aniline with ethyl trifluoroacetate or trifluoroacetic anhydride, followed by reduction with diborane in tetrahydrofuran. Yields are high unless the aniline carries a carboxyl, carbonyl, olefin, or o-nitro substituent. Several new N-substituted trifluoroacetamides and trifluoroethylanilines are reported.

INTRODUCTION

Trifluoroethyl-substituted derivatives of aniline are useful intermediates in the synthesis of dyes and biologically-active compounds [1-3]. They have generally been prepared by the direct alkylation of the desired amine with trifluoroethanol, trifluoroethyl iodide, [4-6] or tris(trifluoroethyl)phosphate [7] or by reduction of an azine by lithium aluminum hydride [8]. The direct alkylations all require rather drastic conditions and generally fail completely when electron-withdrawing substituents are present on the aromatic ring [7]. Reduction of the azine requires isolation of an intermediate that is prone to polymerization [8].

Reduction of the more readily accessible and easily purified 2,2,2-trifluoro-N-arylacetamides appears to be a better approach. Although we had earlier been successful in reducing 2,2,2-trifluoro-N-alkylacetamides with lithium aluminum hydride [9], this reagent was unsatisfactory with the N-aryl compounds and resulted in cleavage of the trifluoroacetyl group rather than reduction.

Recent work has shown that the diborane tetrahydrofuran complex is the reagent of choice for reduction of most amides [10,11]. We have now applied this reducing agent to a number of 2,2,2-trifluoro-N-arylacetamides with generally good results.

RESULTS AND DISCUSSION

Table 1 lists some of the properties of the trifluoroethylanilines produced by the method of borane reduction. Their nuclear magnetic resonance (NMR) spectral properties are shown in Table 2 and chemical analyses in Table 3. The borane reduction method would be expected to fail only where carboxyl, carbonyl, or olefin groups are present [10]. Of these, we have tested only the carboxyl group and find that it is reduced to a methyl group as expected.

TABLE 1

Substituted N-trifluoroethylanilines from borane reduction of trifluoroacetamides

Substituent	Yield		bp (at 100 Pa) or mp (°C)
	Found (%)	Reported* (%)	
None	77.2	50	
3-methoxy	77.4	6	
2-ethoxy	63.0		78-81
5-methoxy-2-methyl	69.6		68-70
3-hydroxy	62.8		88-90
5-hydroxy-2-methyl	54.8		76.3 mp
2,4,6-tribromo	96.5		71.2 mp
2-nitro	5		90.0 mp
3-nitro	70.9		112.2 mp
4-nitro	46.6		116.1 mp
4-methyl†	43.8	60	52-53

*Taken from ref. 7.
†From reduction of 4-carboxy compound.

TABLE 2

NMR spectral properties of substituted N-trifluoroethylanilines

Substituent	δ (ppm)				
	CH_3	NCH_2	OCH_2	NH	ArH
2-ethoxy	1.36T(3) J=6.8	3.56Q* J=8.6	3.92Q* J=6.8	4.28S*	6.60M(4)
			$\underline{OCH_3}$		
5-methoxy-2-methyl	2.20S(3)	3.52Q† J=9.0	3.62S†	4.20S(1)	6.4M(3)
				$\underline{NH,OH}$	
3-hydroxy		3.52Q(2) J=9.0		4.48S(2)	6.08M(3) 6.90T(1)
5-hydroxy-2-methyl	2.20S(3)	3.65Q(2) J=9		4.5S(2)	6.40S(3)
				$\underline{NH}$	
2,4,6-tribromo		3.93Q**		4.13S**	7.70S(2)
2-nitro		4.00M(2)††			7.5M(4)
3-nitro		3.90Q(2) J=9			7.3M(4)
4-nitro		3.98Q(2) J=9			6.70S, 6.87S, 8.00S, 8.17S (4)

*Integrator unable to separately integrate these three resonances, but their total was five as expected.

†These two resonances were not separately integrated, but their total was five as expected.

**These two resonances were not separately integrated, but their total was three as expected.

††This portion of the spectrum consists of two quartets much like those of 3-methoxy-N-trifluorethylaniline and suggests hindered rotation of the trifluoroethyl group [7].

The only other failure that we have encountered so far is with 2,2,2-trifluoro-N-(2'-nitrophenyl)acetamide. The desired product was produced in only about a 5% yield, and the major reaction was cleavage of the trifluoroacetyl group. This result is not an effect of steric hindrance, as is evident from the high yields obtained in the reduction of the o-ethoxy and 2,4,6-tribromo compounds, but is most likely a result of

the ready formation of a cyclic intermediate (see Fig. 1). Such a mechanism would require liberation of a mole of hydrogen during the initial step, which is not normally the case in borane reductions. In fact, the reduction of 2,2,2-trifluoro-N-(2'-nitrophenyl)acetamide appeared to be the most exothermic reaction of the series, and foaming during the addition made the reaction difficult to control. We assume the foaming was due to liberation of hydrogen. The O-trifluoroacetate (see Fig. 1) would be very unstable with respect to hydrolysis and would, during the workup, yield an aci-nitro compound that would readily tautomerize to o-nitroaniline.

Many of the N-substituted trifluoroacetamides used in this work were prepared by aminolysis of ethyl trifluoroacetate, rather than the more usual reaction with trifluoroacetic anhydride. This method, which does not appear to have been reported previously, has the advantages of using the potentially less expensive ester and of avoiding the handling of the corrosive anhydride. However, the method does not work with electronegatively substituted or highly hindered anilines. The amides made by this method are listed in Table 4. Chemical analyses are given in Table 5.

TABLE 3

Microchemical analyses of substituted N-trifluoroethylanilines

Substituent	Formula	Calculated (%)			Found (%)		
		C	H	N	C	H	N
2-ethoxy	$C_{10}H_{12}F_3NO$	54.79	5.52	6.39	54.73	5.48	6.36
5-methoxy-2-methyl	$C_{10}H_{12}F_3NO$	54.79	5.52	6.39	54.51	5.42	6.27
3-hydroxy	$C_8H_8F_3NO$	50.27	4.22	7.33	49.93	3.92	6.87
5-hydroxy-2-methyl*	$C_9H_{10}F_3NO$	52.68	4.91	6.83	53.01	4.98	7.04
2,4,6-tribromo	$C_8H_5Br_3F_3N$	23.33	1.22	3.40	23.56	1.13	3.56
2-nitro	$C_8H_7F_3N_2O_2$	43.65	3.21	12.73	43.81	3.20	12.65
3-nitro					43.50	3.16	12.46
4-nitro					43.62	3.18	12.85

*Prepared by hydrolysis of 5-methoxy-2-methyl-N-trifluoroethylaniline; infrared and NMR spectra showed this product to be identical to one prepared by borane reduction of the acetamide.

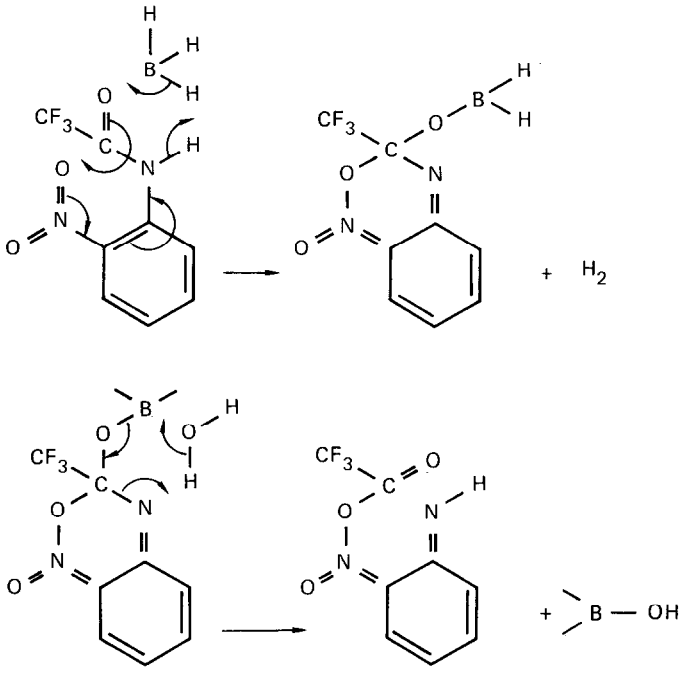

FIG. 1. Mechanism of reduction of 2,2,2-trifluoro-N-(2'-nitrophenyl)acetamide.

EXPERIMENTAL

Melting points, taken on a Mettler Model FP1* apparatus at 2°C/min, are corrected. Boiling points are uncorrected. Nuclear magnetic resonance measurements, in carbon tetrachloride solvent except as noted, were made on a Varian EM360 spectrometer; shifts (δ) are given in ppm relative to internal TMS; S = singlet, D = doublet, T = triplet, Q = quartet, M = complex multiplet; the value in parentheses is the relative area. Coupling constants (J) are given in hertz. Infrared absorption spectra on neat liquids or potassium bromide pellets were taken on a Perkin-Elmer Model 457 grating spectrometer.

*Reference to a company or product name does not imply approval or recommendation of the product by the University of California or the U.S. Department of Energy to the exclusion of others that may be suitable.

TABLE 4

2,2,2-trifluoro-N-phenylacetamides prepared by aminolysis of ethyl trifluoroacetate

Substituent	Yield (%)	Melting point Found (°C)	Melting point Reported* (°C)	NMR spectra δ (ppm) CH_3	NMR spectra δ (ppm) CH_2	NMR spectra δ (ppm) ArH	C=O (cm^{-1})
None	51.6†	90.0	89-90				
3'-methoxy	65.7†	76.6	75				
2'-ethoxy	50.9	60.9	141-2	1.48T(3)	4.13Q(2)	6.9M(4)	1714
					OCH_3		
2'-methyl-	43.0	57.9		2.32S(3)	3.86S(3)	6.80T(2)	
5'-methoxy						8.10S(1)	1710
3'-hydroxy	50.0†	133.1	131-2				
2'-methyl-	54.7	197.4		2.28S(3)**		6.83T(2)**	
5'-hydroxy						7.65S(1)**	1693

*From ref. 12.

†Reported yields [12] by the trifluoroacetic anhydride method are 90-95%, but these are not "isolated" yields.

**In CD_3OD.

TABLE 5

Microchemical analyses of 2,2,2-trifluoro-N-phenylacetamides

Substituents	Formula	Calculated (%) C	Calculated (%) H	Calculated (%) N	Found (%) C	Found (%) H	Found (%) N
2'-ethoxy	$C_{10}H_{10}F_3NO_2$	51.51	4.32	6.01	51.54	4.03	5.67
2'-methyl-5'-methoxy	$C_{10}H_{10}F_3NO_2$	51.51	4.32	6.01	51.27	4.37	6.13
2'-methyl-5'-hydroxy	$C_9H_8F_3NO_2$	49.32	3.68	6.39	49.26	3.80	6.43
2',4',6'-tribromo	$C_8H_3Br_3F_3NO$	22.56	0.71	3.29	22.80	0.66	3.39
4'-carboxy	$C_9H_6F_3NO_3$	46.36	2.59	6.01	46.52	2.61	6.14

Acetamides prepared by aminolysis of trifluoroacetate

(a) 2,2,2-Trifluoro-N-phenylacetamide

Aniline (18.6 g, 0.2 mol) and ethyl trifluoroacetate (28.4 g, 0.2 mol) were refluxed for 24 hr. The cooled reaction mixture was dissolved in

100 ml of diethyl ether, washed twice with 50-ml portions of 1M aqueous hydrochloric acid and once with water. The washed ether solution was dried over anhydrous magnesium sulfate, filtered, and evaporated at room temperature under a stream of argon to yield 19.5 g (51.6%) of acetamide melting at 90.0°C (ref. 12, 89-90°C).

(b) 2,2,2-Trifluoro-N-(3'-methoxyphenyl)acetamide

m-Anisidine (12.3 g, 0.1 mol) and ethyl trifluoroacetate (14.2 g, 0.1 mol) were refluxed for 20 to 30 hr. After the workup described above, the reaction yielded 14.0-14.4 g (63.9-65.7%) of crude trifluoroacetamide, which after recrystallization from benzene melted at 76.6°C (ref. 12, 75°C).

(c) 2,2,2-Trifluoro-N-(2'-ethoxyphenyl)acetamide

This compound was prepared from o-phenetidine in the same manner as the N-phenyl derivative but using a 48-hr reflux period. The yield was 50.9%. After repeated recrystallizations from aqueous ethanol, this material melted at 60.9°C rather than at the 141-2°C reported [12].

(d) 2,2,2-Trifluoro-N-(2'-methyl-5'-methoxyphenyl)acetamide (n.c.)

This compound was prepared from 2-methyl-5-methoxyaniline in the same manner as the N-(2'-ethoxyphenyl) derivative, and the yield was 43.0%. After two recrystallizations from aqueous ethanol, it melted at 57.9°C.

(e) 2,2,2-Trifluoro-N-(3'-hydroxyphenyl)acetamide (n.c.)

This compound was prepared in 50% yield in the same way as the N-(2'-ethoxyphenyl) derivative except that 20 ml of absolute ethanol was added as solvent. After recrystallization from aqueous ethanol, the product melted at 133.1°C (ref. 12, 131-2°C).

(f) 2,2,2-Trifluoro-N-(2'-methyl-5'-hydroxyphenyl)acetamide (n.c.)

This compound was prepared in 54.7% yield from 3-amino-4-methylphenol by the procedure used for the N-(3'hydroxyphenyl) derivative. The analytical sample was recrystallized three times from aqueous ethanol and sublimed at 150°C and 0.1 Pa. The product melted at 197.4°C.

Acetamides prepared by reaction with trifluoroacetic anhydride

(a) 2,2,2-Trifluoro-N-(2',4',6'-tribromophenyl)acetamide (n.c.)

This compound was prepared by dissolving 63.1 g (0.19 mol) of 2,4,6-tribromoaniline in about 700 ml of ether. Trifluoroacetic anhydride (42.0 g, 0.2 mol) was added slowly to the stirred solution at room temperature. After addition was complete, stirring was discontinued and the mixture was stored at room temperature overnight. Evaporation of the ether and drying under vacuum for 2 h at room temperature and 10 Pa yielded 81.8 g (99.4%) of the desired trifluoroacetamide, mp 147.0°C. After two recrystallizations from aqueous ethanol and sublimation at 150°C and 1 Pa, the analytical sample melted at 147.7°C.

(b) 2,2,2-Trifluoro-N-(2'-nitrophenyl)acetamide

This compound was prepared from o-nitroaniline in 95.0% yield by the trifluoroacetic anhydride method, mp 90.4°C (ref. 13, 89-90°C).

(c) 2,2,2-Trifluoro-N-(3'-nitrophenyl)acetamide

This compound was prepared from m-nitroaniline in 38.6% yield by the trifluoroacetic anhydride method, mp 94.2°C (ref. 14, 88°C).

(d) 2,2,2-Trifluoro-N-(4'-nitrophenyl)acetamide

This compound was prepared from p-nitroaniline in nearly quantitative yield by the trifluoroacetic anhydride method, mp 154.1°C (ref. 15, 151.5-153°C).

(e) 2,2,2-Trifluoro-N-(4'-carboxyphenyl)acetamide

This compound was prepared from p-aminobenzoic acid in 95.2% yield by the trifluoroacetic anhydride method, mp above 300°C (ref. 16, 284-5°C). The analytical sample was recrystallized from aqueous ethanol and sublimed at 150°C and 0.1 Pa.

N-trifluoroethylanilines prepared by borane reduction of trifluoroacetamides

(a) N-Trifluoroethylaniline

A solution of 9.46 g (0.05 mol) of 2,2,2-trifluoro-N-phenylacetamide in 50 ml of dried (NaPb alloy) tetrahydrofuran was added under argon over a period of ahout 20 min to a stirred, 1M solution of diborane in tetrahydrofuran (200 ml). The reaction mixture was stirred at room temperature for 2 h, then refluxed for 21 h, and finally cooled to room temperature. Excess hydride was destroyed by careful addition of 5 ml of absolute ethanol followed by 1 ml of water. Concentrated aqueous hydrochloric acid (15 ml) was added, and about 180 ml of the tetrahydrofuran was removed by distillation. The resident was poured into 100 ml of water. This solution was extracted with three 50-ml portions of ether. The combined ether extracts were washed with 25 ml of water, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was distilled to yield 11.5 g of a single cut that boiled at 49-51°C at 100 Pa. Gas chromatography (GC) showed this cut to be a mixture of N-trifluoroethylaniline (58.7%) and 1,4-butanediol (from cleavage of tetrahydrofuran); the calculated yield was 77.2%.

(b) 3-Methoxy-N-trifluoroethylaniline

This compound was prepared in the same way as the N-trifluoroethylaniline. After a forecut boiling at 35-50°C and 100 Pa, distillation yielded 8.01 g of product that boiled at 70-72°C at 100 Pa and that was identical by infrared and NMR spectra and GC retention time to a sample prepared by alkylation with tris(trifluoroethyl)phosphate [7]; GC indicated 98.6% purity (77.4% yield).

(c) 2-Ethoxy-N-trifluoroethylaniline (n.c.)

This compound was prepared similarly. Distillation yielded 6.9 g (63%) of product that boiled at 78-81°C; d_{22} = 1.230 g/cm^3; n_D^{20} = 1.4800 (see also Tables 1 and 2). The analytical sample was purified by GC, using a 3.2-mm by 3-m stainless steel column, packed with 20% SE-30 on 60-70 mesh GC-22 firebrick, at 195°C. Analysis shown in Table 3.

(d) 5-Methoxy-2-methyl-N-trifluoroethylaniline (n.c.)

This compound was prepared similarly. Distillation yielded 7.63 g (69.6%) of product boiling at 68-70°C at 100 Pa; d_{20} = 1.198; $n_D^{21.5}$ = 1.4840 (see also Tables 1, 2); GC (3.2 mm by 2 m stainless-steel column, packed with 20% carbowax 20M on 70-80 mesh Gaschrom R, at 210°C) showed a purity of 99.4%. The analytical sample was purified further by GC (see Table 3).

(e) 3-Hydroxy-N-trifluoroethylaniline (n.c.)

This compound was prepared similarly except that after the ether extracts were washed with water, they were washed with two 50-ml portions of 0.8 N aqueous sodium hydroxide. The sodium hydroxide extracts were washed with 25 ml of ether, acidified to pH less than 2 with concentrated aqueous hydrochloric acid, and reextracted three times with 50-ml portions of ether. These extracts were dried, filtered, and evaporated as usual. Distillation yielded 6.0 g (62.8%) of colorless viscous oil that boiled at 88-90°C at 100 Pa; $n_D^{22.5}$ = 1.5093 (see Tables 1-3).

(f) 5-Hydroxy-2-methyl-N-trifluoroethylaniline (n.c.)

This compound was prepared by borane reduction in the same manner as 3-hydroxy-N-trifluoroethylaniline except that, on evaporation of the final ether extract, the residue solidified and was recrystallized from petroleum ether (bp 75-110°C); yield 5.62 g (54.8%), mp 76.3°C (see Tables 1-3). Infrared and NMR spectra showed this product to be identical to the sample prepared by hydrolysis of 5-methoxy-2-methyl-N-trifluoroethylaniline as follows. The methoxy compound (6.52 g, 30 mmol) was heated under reflux for 4 days with 10 ml of 48% aqueous hydrobromic acid. After cooling to room temperature, the reaction mixture was diluted with 5 ml of water, and the pH was adjusted to 7 by careful addition of concentrated aqueous ammonia. The separated oil crystallized on standing and was filtered off and dried overnight at room temperature and 3 Pa; weight, 5.72 g (92.9%). After recrystallization from petroleum ether (bp 75-110°C) and sublimation at 100°C and 10 Pa, the product melted at 80.7°C.

(g) 2,4,6-Tribromo-N-trifluoroethylaniline (n.c.)

This compound was prepared in the same way as N-trifluoroethylaniline except that evaporation of the dried and filtered ether extracts yielded a

solid, which was recrystallized from aqueous ethanol; yield 15.9 g (96.5%); mp 68.3°C. Two more recrystallizations and sublimation at 80°C and 3 Pa raised the melting point to 71.2°C (see Tables 1-3).

(h) 2-Nitro-N-trifluoroethylaniline (n.c.)

The reduction was carried out in the same way as before except much greater care was required in adding trifluoroacetamide to the diborane solution. The reaction seemed the most exothermic of any and produced much more foaming. Evaporation of the ether extracts yielded 5.5 g of yellow oil. Chromatography on silica gel and elution with carbon tetrachloride gave two fractions, o-nitroaniline (identified by melting point, infrared spectrum, and thin layer chromatography R_f) and the desired product, which after recrystallization from carbon tetrachloride/petroleum ether and sublimation at 100°C and 0.1 Pa, melted at 90.0°C; NO_2 absorptions in the infrared were at 1515 and 1360 cm^{-1}; $R_f(SiO_2/CH_2Cl_2)$ = 0.79 and (SiO_2/toluene) = 0.36. The estimated yield was about 5% (see Tables 1-3). The original reaction mixture was made strongly basic by addition of 15 ml of 50% aqueous sodium hydroxide and was reextracted with ether. Another 4.4 g of o-nitroaniline was isolated from this extract.

(i) 3-Nitro-N-trifluoroethylaniline (n.c.)

This compound was prepared in the same way as N-trifluoroethylaniline. Evaporation of the ether extracts left a yellow solid, which was recrystallized from aqueous ethanol to yield 7.8 g (70.9%) of product melting at 112.2°C; the nitro stretching frequencies were 1545 and 1340 cm^{-1}; R_f (SiO_2/CH_2Cl_2) = 0.86 and (SiO_2/toluene) = 0.53 (see Tables 1 and 2). The analytical sample was sublimed at 130°C and 1 Pa, mp 113.3°C (see Table 3).

(j) 4-Nitro-N-trifluoroethylaniline (n.c.)

This compound was prepared in the same way as the 3-nitro isomer; yield 5.13 g (46.6%); mp 116.1°C; the nitro stretching frequencies were 1600 and 1320 cm^{-1}; R_f (SiO_2/CH_2Cl_2) = 0.77 and (SiO_2/toluene) = 0.16 (see Tables 1-3).

(k) 4-methyl-N-trifluoroethylaniline

2,2,2-trifluoro-N-(4'-carboxyphenyl)acetamide (11.0 g, 0.05 mol) was reduced as described for the phenyl derivative except that 75 ml of tetrahydrofuran was required to dissolve the amide, and the ether extracts were washed twice with 50-ml portions of 0.8 M aqueous sodium hydroxide, followed by 25 ml of water. Drying, filtering, evaporating, and distilling gave two fractions of 4.66 g and 1.82 g that boiled at 43-52°C and 52-53°C at 100 Pa, respectively. Fraction 2 was shown to be 4-methyl-N-trifluoroethylaniline by comparison of GC retention times and infrared and NMR spectra with those of an authentic sample [7]. The GC also showed that Fraction 1 had 51% of the same material; the total calculated yield was 4.14 g (43.8%). The aqueous sodium hydroxide washes were acidified with concentrated hydrochloric acid and reextracted with three 50-ml portions of ether. Drying, filtering, and evaporating left only 0.2 g of oily residue, which was not further identified.

ACKNOWLEDGMENTS

The authors are indebted to M. C. Waggoner of the Lawrence Livermore Laboratory for the microchemical analyses of 2,2,2-trifluoro-N-(2'ethoxyphenyl)-acetamide and 3-hydroxy-N-trifluoroethylaniline. Other microchemical analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. This work was performed under the auspices of the U.S. Department of Energy by the Lawrence Livermore Laboratory under contract number W-7405-ENG-48.

REFERENCES

1 J. B. Dickey, E. B. Towne, M. S. Bloom, G. J. Taylor, H. M. Hill, R. A. Corbitt, M. A. McCall, W. H. Moore, and D. G. Hedberg, Ind. Eng. Chem. 45 (1953) 1730.

2 G. Kremer, J. Pechmeze, and R. Sureau, Ger. Offen. 2,430,778 (1975).

3 V. Dupre, J. Pechmeze, and R. Sureau, Ger. Offen. 2,513,801 (1975).

4 J. B. Dickey, U.S. Pat. 2,516,106 (1950).

5 J. B. Dickey, U.S. Pat. 2,618,630 (1952).

6 J. B. Dickey, E. B. Towne, M. S. Bloom, G. J. Taylor, H. M. Hill, R. A. Corbitt, M. A. McCall, and W. H. Moore, Ind. Eng. Chem. 46 (1954) 2213.

7 E. R. Bissell, J. Fluorine Chem. 9 (1977) 5.

8 Yu. V. Zeifman, N. P. Gambayan, and I. L. Knunyants, Izv. Akad. Nauk SSSR, Ser. Khim. (1965) 450.

9 E. R. Bissell and M. Finger, J. Org. Chem. 24 (1959) 1256.

10 H. C. Brown, P. Heim, and N. M. Yoon, J. Am. Chem. Soc. 96 (1970) 1637.

11 H. C. Brown, Boranes in Organic Chemistry, Cornell U. Press, Ithica, N.Y. 1972, Chs. 12 and 13.

12 N. Pailer and W. J. Huebsch, Monatsh. Chem. 97 (1966) 1541.

13 K. C. Rutherford, S. Y-S. Ing., and R. J. Thilbert, Can J. Chem. 43 (1965) 541.

14 M. J. Saxby, Org. Mass Spectrom. 2 (1969) 835.

15 E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, J. Chem. Soc. (1952) 4014.

16 H. A. Staab and G. Walther, Ber. 95 (1962) 2070.