[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

SOME AROMATIC TRIFLUOROMETHYL DERIVATIVES. THE ROSENMUND REDUCTION OF TRIFLUOROMETHYLBENZOIC ACIDS[1]

ALFRED BURGER AND EDWIN D. HORNBAKER[2]

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In connection with a chemotherapeutic testing program of trifluoromethyl substituted benzalimines, amides, sulfonamides, and related compounds, we wished to use *p*-trifluoromethylbenzaldehyde as an intermediate. This compound had been prepared previously by the Stephen method from *p*-trifluoromethylbenzonitrile (1), and we considered the applicability of the Rosenmund reduction to this case. For this reaction, the known resistance of the trifluoromethyl group to hydrogenation under different conditions, and the stability of the group to hydrogen chloride at elevated temperatures had to be considered.

Haas and Bender (2) reduced ethyl *p*-trifluoromethylbenzoate to *p*-trifluoromethylbenzyl alcohol with lithium aluminum hydride, and *o*- and *p*-nitrobenzotrifluoride could be hydrogenated uneventfully over a nickel catalyst to the corresponding trifluoromethylaniline derivatives (3). High pressure hydrogenations of trifluoromethyl compounds have also been reported. Jones hydrogenated *o*-methyltrifluoroacetophenone in the presence of ammonia to 1,1,1-trifluoro-2-amino-2-(*o*-tolyl)ethane (4, 5), and Nes and Burger (5) carried out a similar reduction of trifluoromethyl benzyl ketone to 1,1,1-trifluoro-2-amino-3-phenylpropane. Indeed, when trifluoromethyl benzyl ketoxime was hydrogenated the trifluoromethyl group remained unaffected whereas both the oxime group and the aromatic ring suffered reduction.

The literature also reports that the trifluoromethyl group undergoes hydrolytic cleavage even under apparently anhydrous conditions under the influence of acidic reagents. Especially various concentrations of strong sulfuric acid split CF_3 groups to carboxyl (6). Hot hydrohalic acids also lead to hydrolysis under certain conditions (6, 7).

It has now been shown that both *m*- and *p*-trifluoromethylbenzoyl chlorides undergo the Rosenmund reduction using a quinoline-sulfur-poisoned palladium catalyst in boiling xylene, and give yields of 75–80% of the respective aldehydes. *m*-Trifluoromethylbenzaldehyde had previously been prepared by the Stephen method (8) and by the Bouveault reaction (9).

Several of the derivatives listed in Table I have been shown to be inactive in experimental amebiasis, and against tubercle bacilli in the presence of serum.

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[2] Parke, Davis and Co. Fellow.

TABLE I
DERIVATIVES OF AMINOBENZOTRIFLUORIDE

NAME	APPEARANCE, CRYSTALS	RECRYSTALLIZING SOLVENT	M.P., °C.	COMPOSITION	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
p-Benzamidobenzotrifluoride	Leaflets	Ethanol	205–206	$C_{14}H_{10}F_3NO$	63.39	3.80		63.54	3.72	
p-Benzenesulfamidobenzotrifluoride	Colorless	Petroleum ether-benzene	101–101.5	$C_{13}H_{10}F_3NO_2S$			4.65			4.92
p-(4-Nitrobenzamido)benzotrifluoride	Pale yellow	Dil. ethanol	213.5–215.5	$C_{14}H_9F_3N_2O_3$			9.03			8.78
p-(3-Nitrobenzenesulfamido)-benzotrifluoride	Leaflets	Dil. ethanol	110.5–111	$C_{13}H_9F_3N_2O_4S$	45.09	2.62		45.30	2.59	
p-(4-Acetamidobenzenesulfamido)benzotrifluoride[a]	Colorless	Dil. ethanol	192–193.5	$C_{15}H_{13}F_3N_2O_3S$	50.27	3.66		49.73	3.44	
p-(4-Nitrobenzenesulfamido)-benzotrifluoride	Pale yellow	Dil. ethanol	150–150.5	$C_{13}H_9F_3N_2O_4S$	45.09	2.62		45.76	2.59	
N-(4-Trifluoromethylphenyl)-phthalamidic acid	Colorless	Dil. acetone	256.5–257.5[b]	$C_{15}H_{10}F_3NO_3$	58.25	3.26		58.53	3.34	
4,4′-Bis-(trifluoromethyl)benzalaniline[c]	Pale yellow	Dil. ethanol	87.5–88.5	$C_{15}H_9F_6N$	56.79	2.86		56.68	2.95	
N-Allyl-N′-(3-trifluoromethylphenyl)thiourea[d]	Needles	Dil. ethanol	94–94.5	$C_{11}H_{11}F_3N_2S$	50.76	4.26		50.58	4.48	
N-Allyl-N′-(4-trifluoromethylphenyl)thiourea[e]	Needles	Ethanol	142.5–143.5	$C_{11}H_{11}F_3N_2S$	50.76	4.26		50.61	4.46	

[a] Mentioned by DRAKE, *et al.*, *J. Am. Chem. Soc.*, **68**, 1602 (1946). [b] Sintered at 211°. [c] Prepared by heating equivalent amounts of *p*-trifluoromethylbenzaldehyde and *p*-aminobenzotrifluoride in ethanol solution for four hours. Yield, 91%. [d] Prepared by refluxing *m*-aminobenzotrifluoride and allyl isothiocyanate in ethanol for 16 hours. Yield, 75%. [e] From *p*-aminobenzotrifluoride as in *c*. Yield, 91%.

evaluation indicated above. The *p*-aminobenzotrifluoride used in our work was prepared according to directions kindly furnished by Dr. Glenn C. Finger of the Illinois State Geological Survey.

EXPERIMENTAL[3]

p-Trifluoromethyl-benzamides and -sulfonamides. The amides and sulfonamides were prepared by adding 0.031 mole of acid chloride to a solution of 5 g. (0.031 mole) of *p*-aminobenzotrifluoride (10) in 10 ml. of pyridine, the temperature being kept below 45°. The mixture was then heated at 80–90° for 30–45 minutes, cooled, and the reaction product was filtered. In those cases wherein precipitation did not immediately occur, the mixture was stirred, and if necessary, shaken for four hours with 5% aqueous hydrochloric acid. The resulting precipitates were filtered and recrystallized from the solvents indicated in Table I.

N-(4-Trifluoromethylphenyl)phthalamidic acid. p-Aminobenzotrifluoride (5 g., 0.031 mole) was added with stirring to a solution of 6.9 g. (0.047 mole) of phthalic anhydride in 112 g. of glacial acetic acid at 30°. The precipitate which formed immediately was filtered, washed with water, dissolved in dilute sodium carbonate solution, and acidified. The yield was 4.7 g. (49%). Heating of an acetone solution resulted in the formation of a base-insoluble material, perhaps the phthalimide derivative.

m-Trifluoromethylbenzoic acid. The Grignard reagent obtained from 10.6 g. of magnesium and 94.9 g. of *m*-bromobenzotrifluoride (11) in 250 ml. of dry ether was poured with stirring onto 175 g. of Dry Ice, and the adduct was decomposed with 500 ml. of ice-cold 3.5% hydrochloric acid. The ether solution was washed with 3.5% hydrochloric acid, then with sodium bicarbonate solution. The latter was treated with Darco, filtered, and acidified. It yielded 60.6 g. (76.5%) of *m*-trifluoromethylbenzoic acid, m.p. 102–105°. Swarts (12) reports m.p. 103°.

Reduction of p-trifluoromethylbenzoyl chloride. p-Trifluoromethylbenzoic acid, prepared from *p*-bromobenzotrifluoride (13), was converted to *p*-trifluoromethylbenzoyl chloride (2) (b.p. 86–87°/16 mm.) in 80.5% yield by the action of thionyl chloride.

Hydrogen was passed into a stirred, refluxing mixture of 16.2 g. of *p*-trifluoromethylbenzoyl chloride, 100 ml. of dry xylene, 1.62 g. of 5% palladium-on-barium sulfate catalyst, and 0.16 ml. of a 10% quinoline-sulfur regulator solution until hydrogen chloride was no longer evolved (95% conversion). The solution was cleared with Norit, filtered, diluted with 100 ml. of ether, and shaken with 200 ml. of saturated sodium bisulfite solution for 12 hours. The sodium bisulfite addition product was filtered, washed with ether, decomposed with sodium carbonate solution, and the *p*-trifluoromethylbenzaldehyde was extracted with ether. Yield of crude product, 9.76 g. (72%). The *semicarbazone* crystallized as colorless leaflets from ethanol, m.p. 193.5–194.5°.

Anal. Calc'd for $C_9H_8F_3N_3O$: C, 46.76; H, 3.49.
Found: C, 47.02; H, 3.56.

The *3-thiosemicarbazone* melted at 172–173°. The literature (1) reports m.p. 167–168°.

m-Trifluoromethylbenzaldehyde. This isomer was prepared in 81% yield from *m*-trifluoromethylbenzoyl chloride as described for the *p*-isomer above. The aldehyde boiled at 79–83° (20 mm.). The 2,4-dinitrophenylhydrazone melted at 260–261°. Gilman, *et al.* (9) report m.p. 259–260°.

SUMMARY

m- and *p*-Trifluoromethylbenzoyl chloride have been reduced by the Rosenmund method to *m*- and *p*-trifluoromethylbenzaldehyde, respectively.

Several acyl and arylsulfonyl derivatives of *p*-aminobenzotrifluoride have been prepared for chemotherapeutic tests.

Charlottesville, Va.

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[3] All melting points are corrected.

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