Organolithium Intermediates from 1,4-Disubstituted Tetrafluorobenzene Compounds

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Lithium-hydrogen and lithium-bromine interconversion studies on various 2,3,5,6-tetrafluorobenzene compounds have been done. The solvent (tetrahydrofuran *vs.* diethyl ether) has a pronounced effect in regard to degree of metalation. Reactions of the organolithium intermediates as carbonation, hydrolysis, sulfurization, and chlorination have been successfully carried out.

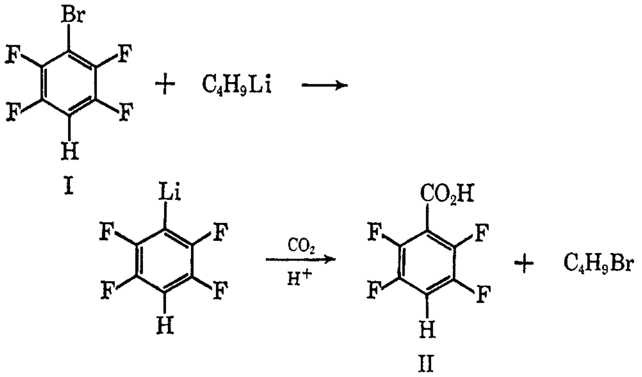
Aryl organolithium reagents have been conveniently prepared through the metal-halogen interconversion reaction[1] and less frequently through the metal-hydrogen interconversion.

$$ArBr(H) + n\text{-}C_4H_9Li \longrightarrow ArLi + C_4H_9Br(H)$$

These two reactions have been recently applied to the synthesis of pentafluorophenyllithium *via* lithium-bromine interconversion[2] and later *via* lithium-hydrogen interconversion.[3] We have recently reported the latter reaction and have made the following observations relative to the nature of these reactions: (a) metal-hydrogen interconversion is faster and more complete for *n*-butyllithium than for ethylmagnesium bromide; (b) the interconversions are faster in tetrahydrofuran (THF) solvent than in diethyl ether; and (c) the *p*-hydrogen atoms in 1,2,4,5-tetrafluorobenzene are more reactive than the *o*-hydrogen atoms in 1,2,3,4-tetrafluorobenzene towards interconversion with *n*-butyllithium.

We now report further studies in the preparation of various organolithium derivatives of 2,3,5,6-tetrafluorobenzene compounds in which we have examined the following: (a) bromine *vs.* hydrogen interconversions with *n*-butyllithium; (b) solvent effect (tetrahydrofuran and diethyl ether) on degree of interconversion; and (c) reactions of various 2,3,5,6-tetrafluorophenyllithium intermediates. The degree of metalation in most cases was determined by carbonating the organolithium intermediates to the fluoroaromatic acids.

Lithium-Bromine *vs.* Lithium-Hydrogen Interconversions.—The interconversion reactions can be conveniently followed by the use of Color Test IIA[4] which indicates the presence of *n*-butyllithium. Pentafluorophenyllithium can be prepared conveniently through either a lithium-bromine or lithium-hydrogen interconversion. Both methods in our laboratory have produced pentafluorobenzoic acid (67-83%) on carbonation either in tetrahydrofuran or diethyl ether.



Both interconversions take place quite rapidly. The relative rate of interconversion was determined by allowing equimolar quantities of pentafluorobromobenzene, pentafluorobenzene, and *n*-butyllithium to react in tetrahydrofuran. Carbonation of the reaction mixture produced pentafluorobenzoic acid (92% based on *n*-butyllithium) while the vapor phase chromatographic analysis of the nonacidic product indicated only unreacted pentafluorobenzene. No unreacted pentafluorobromobenzene was detected. The reaction between 2,3,5,6-tetrafluorobromobenzene with 1 equiv. of *n*-butyllithium in diethyl ether gave as the major product 2,3,5,6-tetrafluorobenzoic acid (71%) with only a trace amount of tetrafluoroterephthalic acid. No indication of 4-bromo-2,3,5,6-tetrafluorobenzoic acid formation was noted. Further evidence of the greater reactivity of the bromo derivative will be subsequently shown.

Solvent Effects.—We have examined tetrahydrofuran and diethyl ether[5] as reaction media for the preparation of various fluorophenyllithium intermediates. Where only one reactive site (Br or H) is present, the interchange reactions in tetrahydrofuran or diethyl ether are rapid. If, however, two reactive, *para*-oriented sites (Br or H) are present, the yields of the organolithium intermediate (mono- or dilithio) can be varied and depend on solvents and functional group. Difficulty has been experienced in producing a single desired organolithium intermediate and the products are usually mixtures with one type predominating. Only in one case thus far, 1,4-dibromotetrafluorobenzene, have the proper conditions been found which produce a single organolithium derivative in high yields. It is possible that further studies on variations of solvent, temperature, time, and mode of addition may lead to the preparation of predominantly mono- or dilithio species as desired. Table I is a summary of yields of acids formed as a result of the interconversion studies. It can be seen that the use of diethyl ether generally favors monointerconversion while tetrahydrofuran favors diinterconversion. The availability of these organolithium intermediates provides a convenient method for preparing various difunctional tetrafluorobenzene compounds.

Reactions of Fluorophenyllithium Intermediates.—The fluorophenyllithium derivatives prepared undergo

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(1) R. G. Jones and H. Gilman, *Org. Reactions*, **4**, 339 (1951).

(2) P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 3227 (1962).

(3) R. J. Harper, Jr., E. J. Soloski, and C. Tamborski, *J. Org. Chem.*, **29**, 2385 (1964).

(4) H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, **62**, 1847 (1940).

(5) Since the *n*-butyllithium used in this study was commercially prepared (Foote Mineral Co., Exton, Pa.) in *n*-hexane, the true comparison of solvent systems should be indicated as hexane-tetrahydrofuran and hexane-diethyl ether.

TABLE I

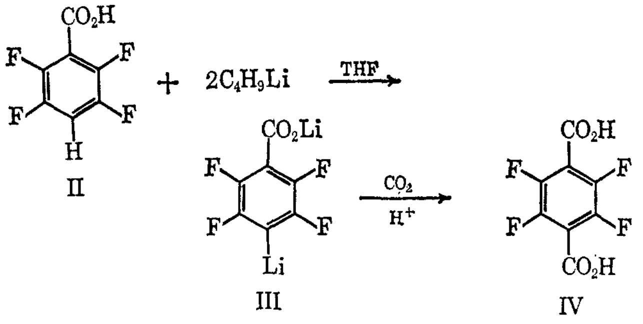
AVERAGE YIELD OF ACIDS[a]

Expt.	Reactants	—% monoacid/% diacid— Ether	THF
1	p-$Br_2C_6F_4$ + $2n$-BuLi	0/52	0/92
2	p-$H_2C_6F_4$ + $2n$-BuLi	33/38[b]	7/70[b]
3	p-$Br_2C_6F_4$ + n-BuLi	71/21	51/. .[c]
4	p-$H_2C_6F_4$ + n-BuLi	85/2	36/63
5	p-$HBrC_6F_4$ + n-BuLi	71/trace[d]	. . .

[a] Yields reported are on pure products. In general the crude yields were considerably higher. The monoacids could be separated conveniently from the diacids by extraction with petroleum ether (b.p. 90–120°) in which the diacid is insoluble. [b] Results originally reported in ref. 3. [c] Reaction was hydrolyzed to yield 2,3,5,6-tetrafluorobromobenzene. Since 2,3,5,6-tetrafluorodilithiobenzene on hydrolysis would yield 2,3,5,6-tetrafluorobenzene, no attempt was made to isolate this product resulting from diinterconversion. [d] The monoacid isolated was 2,3,5,6-tetrafluorobenzoic acid.

some of the conventional reactions of aryllithium reagents. Carbonation yields the fluoroarylcarboxylic acids (Table I). Hydrolysis affords the hydrofluoroaromatic compound. Thus, the reaction between equimolar quantities of n-butyllithium and 1,4-dibromo-2,3,5,6-tetrafluorobenzene yields on hydrolysis the hydrobromotetrafluorobenzene. This monobromo compound in turn forms the monolithio derivative which yields after carbonation 2,3,5,6-tetrafluorobenzoic acid.

The presence of certain reactive sites other than hydrogen and bromine does not seem to offer any difficulty in preparing 2,3,5,6-tetrafluorophenyllithium



intermediates. Thus, the reaction between 2 equiv. of n-butyllithium and 2,3,5,6-tetrafluorobenzoic acid in tetrahydrofuran, on carbonation, yielded tetrafluoroterephthalic acid in 94% yield. In a similar manner, the organolithium derivative III and elemental sulfur afforded 4-thiol-2,3,5,6-tetrafluorobenzoic acid in 75.0% yield. Reaction between chlorine and the organolithium derivative III yielded 4-chloro-2,3,5,6-tetrafluorobenzoic acid.

Apparently, from the above examples, the fluorophenyllithium derivatives behave as typical aryllithium intermediates. There are, however, some cases where they do not behave similarly. Attempts to treat the organolithium intermediate III with oxygen at temperatures of −65 (18 hr.) and 0° (5.5 hr.) in tetrahydrofuran to yield the 4-hydroxy-2,3,5,6-tetrafluorobenzoic acid were unsuccessful. The reactant II was recovered in 83% yield with no indication of a phenolic[6] compound being formed. This lack of reaction does, however, indicate the thermal stability of the intermediate organolithium compound III. Under similar conditions, pentafluorophenyllithium in tetrahydrofuran at 0° polymerizes to a high-melting intractable solid.[7]

Further research on the synthesis and reactions of organolithium intermediates prepared from 1,2,3,4-tetrafluorobenzene and 1,2,3,5-tetrafluorobenzene is in progress.

Experimental Section

All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen. All melting points are uncorrected. Tetrahydrofuran was freshly distilled from sodium. Vapor phase chromatographic analyses were carried out on a F & M Model 500 gas chromatogram. A 6-ft. Apiezon L on Chromasorb P (60–80 mesh) column using helium carrier gas at about 60 cc./min. was used. The temperature was programmed at 5.6°/min.

Tetrafluoroterephthalic Acid from 1,4-Dibromo-2,3,5,6-tetrafluorobenzene.—A solution of 1,4-dibromo-2,3,5,6-tetrafluorobenzene (15.4 g., 0.05 mole) in 43 ml. of tetrahydrofuran was added, during 10 min., to a stirred solution of n-butyllithium (0.10 mole, 67 ml. of a hexane solution) and 107 ml. of tetrahydrofuran maintained at −65°. The stirred mixture was maintained below −65° for 45 min. Color Test IIA[4] was negative. Carbon dioxide was passed slowly through the reaction for 1 hr. The mixture was hydrolyzed with 125 ml. of 6 N hydrochloric acid and phase separated. The organic layer was combined with ether extracts of the aqueous layer. The organic layer was extracted with 5% sodium carbonate solution. The sodium carbonate solution was acidified with hydrochloric acid. Extraction with ether followed by drying and evaporation of solvent yielded 10.9 g. (92%) of tetrafluoroterephthalic acid, m.p. 276–278° (lit.[3] m.p. 281–282°). The infrared spectrum of this material was identical with that of an authentic sample.

When the above reaction was carried out in diethyl ether, in place of tetrahydrofuran, tetrafluoroterephthalic acid was obtained in a 52% yield.

4-Bromo-2,3,5,6-tetrafluorobenzoic Acid.—n-Butyllithium (83.8 ml. of a hexane solution, 0.129 mole) was added dropwise over a period of 2 hr., to a precooled solution (−65°) of 1,4-dibromo-2,3,5,6-tetrafluorobenzene (40.0 g., 0.129 mole) in 300 ml. of anhydrous diethyl ether. Color Test IIA was negative 10 min. after addition was complete. The mixture was then carbonated by bubbling carbon dioxide through the reaction. The reaction mixture was allowed to warm to room temperature with continued carbonation. When the solution reached room temperature, it was hydrolyzed with 300 ml. of 6 N hydrochloric acid and phase separated. The acid layer was washed three times with 100-ml. portions of diethyl ether which were combined with the organic layer and dried over magnesium sulfate. After drying, the ether was removed by distillation yielding 32.95 g. of crude material, m.p. 148–203°. This crude material was slurried with n-hexane. The insoluble material, 29.60 g., m.p. 147.5–212°, was filtered. The filtrate was concentrated to yield 0.28 g. of crude 4-bromo-2,3,5,6-tetrafluorobenzoic acid, m.p. 137.5–143°. Distillation of the filtrate yielded 1.90 g. of starting material, 1,4-dibromo-2,3,5,6-tetrafluorobenzene.

The above n-hexane insolubles, 29.60 g., were placed in a Soxhlet extractor and extracted with petroleum ether (b.p. 90–120°). Concentration of the petroleum ether extracts yielded 23.46 g. (70.8%) of 4-bromo-2,3,5,6-tetrafluorobenzoic acid, m.p. 144.5–145.5°.

Anal. Calcd. for $C_7HBrF_4O_2$: C, 30.77; H, 0.37; Br, 29.27; F, 27.84. Found: C, 31.03; H, 0.31; Br, 29.21; F, 28.27.

The petroleum ether insoluble material, 7.0 g. (21.1%), m.p. 277.5–278.5°, was identified by mixture melting point determination and infrared analysis as tetrafluoroterephthalic acid.

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(6) E. Muller and T. Topel [*Ber.*, **B72**, 273 (1939)] have reported isolating an 18% yield of phenol from the oxidation of phenyllithium.

(7) The infrared spectra of the high-melting intractable solids show a similarity to the polymeric materials reported by E. J. P. Fear, J. Thrower, and M. A. White, XIXth International Congress of Pure and Applied Chemistry, London, July 1963. These materials appear to be mostly *para*-oriented polyfluorophenylene polymers.

2,3,5,6-Tetrafluorobromobenzene.—*n*-Butyllithium (100 ml. of a hexane solution, 0.15 mole) was added during 1 hr. to a stirred solution of 1,4-dibromo-2,3,5,6-tetrafluorobenzene (46.2 g., 0.15 mole) in 300 ml. of tetrahydrofuran maintained at −65°. Immediately after the addition was completed, Color Test IIA was negative. After 14 min. the black mixture was hydrolyzed with 200 ml. of 2 *N* hydrochloric acid. The organic layer was washed repeatedly with water and dilute hydrochloric acid. The dried organic layer was distilled on a spinning-band column, yielding 17.6 g. (51%) of 2,3,5,6-tetrafluorobromobenzene, b.p. 143–143.5°, n^{20}_{D} 1.4691.

Anal. Calcd. for C_6HBrF_4: C, 31.47; H, 0.44; Br, 34.90; F, 33.19. Found: C, 31.59; H, 0.65; Br, 34.70; F, 33.01.

By sublimation the pot residue yielded 8.5 g. (18%) of unreacted 1,4-dibromo-2,3,5,6-tetrafluorobenzene as characterized by a mixture melting point determination with an authentic sample and by infrared analysis.

2,3,5,6-Tetrafluorobenzoic Acid from 1,2,4,5-Tetrafluorobenzene.—*n*-Butyllithium (65 ml. of a hexane solution, 0.1 mole) was added dropwise to a precooled (−65°) solution of 1,2,4,5-tetrafluorobenzene (15.01 g., 0.1 mole) in 300 ml. of anhydrous diethyl ether. Addition of the *n*-butyllithium required 65 min. Twenty minutes after the addition was complete, Color Test IIA was negative. The reaction mixture was stirred an additional 45 min. and then carbonated by bubbling carbon dioxide through the reaction. After 15 min. the ice bath was removed and the reaction mixture warmed to room temperature, with continued carbonation. The mixture was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid and phase separated, and the organic layer was dried over magnesium sulfate. The ether was removed by distillation, yielding 18.10 g. (93.2%) of crude 2,3,5,6-tetrafluorobenzoic acid. The crude acid was placed in a Soxhlet apparatus and extracted, using petroleum ether. From the solvent was obtained 16.5 g. (85.0%) of pure 2,3,5,6-tetrafluorobenzoic acid, m.p. 152–154° (lit.[8] m.p. 154°). The petroleum ether insolubles afforded 0.45 g. (0.0019 mole) of tetrafluoroterephthalic acid, m.p. 273–276°, which was identified by infrared analysis.

When the above reaction was carried out in tetrahydrofuran in place of diethyl ether, 2,3,5,6-tetrafluorobenzoic acid was obtained in 36.0% yield in addition to a 63.0% yield of tetrafluoroterephthalic acid.

2,3,5,6-Tetrafluorobenzoic Acid from 2,3,5,6-Tetrafluorobromobenzene.—*n*-Butyllithium (65 ml. of a hexane solution, 0.1 mole) was added dropwise to a precooled (−65°) solution of 2,3,5,6-tetrafluorobromobenzene (22.90 g., 0.1 mole) in 300 ml. of anhydrous diethyl ether. Addition of the *n*-butyllithium required 38 min. Thirty minutes after the addition was complete, Color Test IIA was negative. The reaction mixture was stirred an additional hour and then carbonated by bubbling carbon dioxide through the reaction. After 1 hr. the reaction mixture was allowed to warm to room temperature, with continued carbonation. The mixture was then hydrolyzed with 200 ml. of 6 *N* hydrochloric acid and phase separated, and the organic layer was dried over magnesium sulfate. The ether was removed by distillation, yielding 13.8 g. (71.1%) of 2,3,5,6-tetrafluorobenzoic acid, m.p. 152–154° (lit.[8] m.p. 154°).

From the petroleum ether insolubles was isolated a trace amount of crude tetrafluoroterephthalic acid, m.p. 271–275°, which was identified by infrared analysis.

Tetrafluoroterephthalic Acid from 2,3,5,6-Tetrafluorobenzoic Acid.—A solution of 2,3,5,6-tetrafluorobenzoic acid (19.4 g., 0.1 mole) in 40 ml. of tetrahydrofuran was added dropwise to a precooled (−65°) solution of *n*-butyllithium (135 ml. of a hexane solution, 0.2 mole) in 270 ml. of tetrahydrofuran. Addition of the 2,3,5,6-tetrafluorobenzoic acid solution required 15 min. Fifteen minutes after the addition was complete, Color Test IIA was negative. The reaction mixture was stirred an additional 35 min. and then carbonated by bubbling carbon dioxide through the reaction mixture. After 0.5 hr. the reaction mixture was allowed to warm to room temperature with continued carbonation. The mixture was then hydrolyzed with 300 ml. of 6 *N* hydrochloric acid and phase separated, and the organic layer was dried over magnesium sulfate. The ether was removed by distillation, yielding 22.39 g. (94.0%) of tetrafluoroterephthalic acid, m.p. 276–278° (lit.[3] m.p. 281–282°). A mixture melting point with an authentic sample showed no depression. The infrared spectrum was also identical with that of an authentic sample.

4-Thiol-2,3,5,6-tetrafluorobenzoic Acid.—A solution of 2,3,5,6-tetrafluorobenzoic acid (9.87 g., 0.051 mole) in 30 ml. of tetrahydrofuran was added dropwise to a precooled (−65°) solution of *n*-butyllithium (65 ml. of a hexane solution, 0.1 mole) in 200 ml. of tetrahydrofuran. Addition of the 2,3,5,6-tetrafluorobenzoic acid required 16 min. Forty-five minutes after the addition was complete, Color Test IIA was negative. After 23 additional minutes, 1.64 g. (0.051 mole) of sulfur was added to the reaction mixture, causing the color to change gradually to green and then to deep yellow. The reaction mixture was stirred an additional 22 hr. before Color Test I[9] was negative. The mixture was then allowed to warm to room temperature, hydrolyzed with 150 ml. of 6 *N* hydrochloric acid, and phase separated, and the organic layer was dried over magnesium sulfate. The ether was removed by distillation and the crude material remaining was recrystallized from petroleum ether, yielding 7.50 g. (68.7%) of yellow crystalline 4-thiol-2,3,5,6-tetrafluorobenzoic acid, m.p. 155–157°.

Anal. Calcd. for $C_7H_2F_4O_2S$: C, 37.18; H, 0.89; F, 33.60; S, 14.18. Found: C, 37.25; H, 0.95; F, 32.75; S, 14.25.

4-Chloro-2,3,5,6-tetrafluorobenzoic Acid.—A solution of 2,3,5,6-tetrafluorobenzoic acid (3.88 g., 0.02 mole) in 25 ml. of anhydrous diethyl ether was added dropwise to a precooled (−65°) solution of *n*-butyllithium (26 ml. of a hexane solution, 0.04 mole) in 125 ml. of anhydrous diethyl ether. Addition of the 2,3,5,6-tetrafluorobenzoic acid required 2 min. Thirty minutes after the addition was complete, Color Test IIA was negative. The reaction mixture was stirred an additional 30 min. Chlorine gas was slowly bubbled below the surface of the reaction while keeping the temperature at −65°. After 30 min. Color Test I was negative. Addition of chlorine was discontinued, and the reaction mixture was allowed to stir an additional 1 hr. The reaction was then allowed to warm to room temperature, hydrolyzed by addition of 150 ml. of 6 *N* hydrochloric acid, and phase separated, and the organic layer was dried over magnesium sulfate. The dried ether solution was distilled to remove the ether solvent. A yellow viscous liquid, 4.3 g., remained. This material was added to warm petroleum ether (b.p. 60–90°), which on cooling yielded the crude product. Another recrystallization from petroleum ether (b.p. 60–90°) afforded the desired product 4-chloro-2,3,5,6-tetrafluorobenzoic acid, m.p. 128–130°.

Anal. Calcd for $C_7HClF_4O_2$: C, 36.79; H, 0.44; F, 33.25; Cl, 15.51. Found: C, 36.37; H, 0.65; F, 33.09; Cl, 15.15.

Competitive Reaction of Pentafluorobenzene and Pentafluorobromobenzene with *n*-Butyllithium.—To a solution of pentafluorobenzene (16.8 g., 0.1 mole) and pentafluorobromobenzene (24.7 g., 0.1 mole) in 300 ml. of diethyl ether maintained at −65°, was added a solution of *n*-butyllithium (0.10 mole, 67 ml. of a hexane solution) over a period of 2.5 hr. After Color Test IIA was negative, carbon dioxide was passed slowly through the reaction for 1 hr. The mixture was hydrolyzed with 200 ml. of 6 *N* hydrochloric acid and phase separated, and the ether layer was dried. A sample of the ether solution was analyzed *via* vapor phase chromatography. Analysis indicated pentafluorobenzene and pentafluorobenzoic acid, but no pentafluorobromobenzene, were present. The dried ether layer was aspirated to yield pentafluorobenzoic acid, 19.7 g. (93%).

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(8) D. J. Alsop, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1801 (1962).

(9) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).