Journal of Organometallic Chemistry
Elsevier Publishing Company Amsterdam
Printed in The Netherlands

CERTAIN REACTIONS OF 2-BROMO-3,4,5,6-TETRAFLUOROPHENYL-LITHIUM

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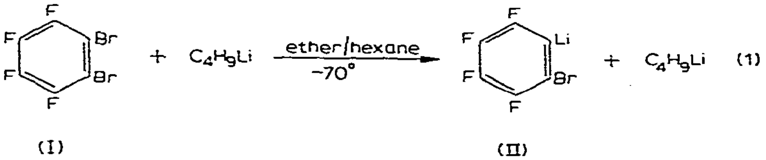
(Received March 31st, 1967; in revised form May 11th, 1967)

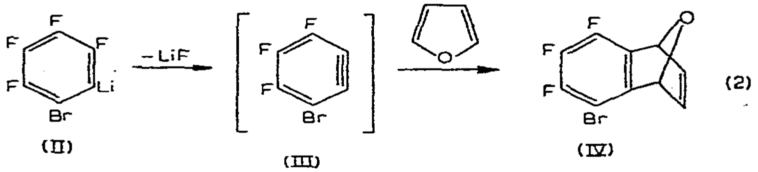
Metal–halogen interconversion reactions have been used successfully in the preparation of perfluorophenyllithium compounds[1]. This general reaction has been extended to many other perfluoroaryllithium compounds. One such compound, 2-bromotetrafluorophenyllithium (II) has been recently[2,3,4,5] reported and used as an intermediate for the preparation of 2-bromotetrafluorophenyl derivatives. We would like to describe in more detail our studies on the synthesis and reactions of this versatile intermediate.

The organolithium compound (II) is conveniently prepared according to the following:

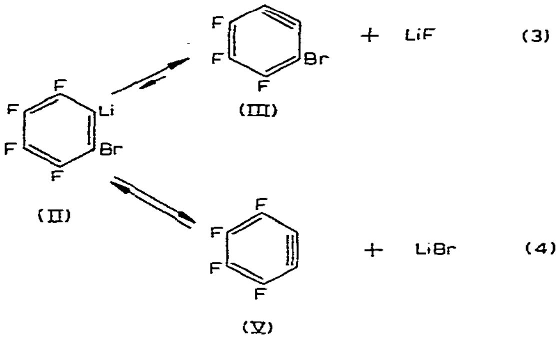


The metal–halogen interconversion was followed by withdrawing samples periodically for vapor phase chromatographic (VPC) analysis. The interconversion is extremely rapid, being 100% complete within one minute. With an equimolar ratio of (I) to n-butyllithium, no disubstitution was detected, indicating a high reactivity of the bromine towards interconversion reactions. The absence of any *o*-dilithiotetrafluorobenzene was inferred by noting that there was no 1,2,3,4-tetrafluorobenzene detected when the organolithium compound was hydrolyzed at −70°. The organolithium compound (II) was stable for at least 24 hours at −70°. No decomposition was noted when the reaction mixture was warmed to −27° and kept at this temperature for 6 hours. However, on raising the temperature to 0°, within 4 hours decomposition of the organolithium (II) was noted. Analysis by VPC indicated a complex mixture of at least 14 components of various peak areas. Efforts to characterize the major peaks are in progress.

If (II) is prepared in furan rather than in diethyl ether as the solvent and allowed to warm to room temperature, the resulting product, 1,2,3-trifluoro-4-bromo-5,8-epoxy-5,8-dihydronaphthalene (IV) (~91%), indicates the following overall reactions had occurred:

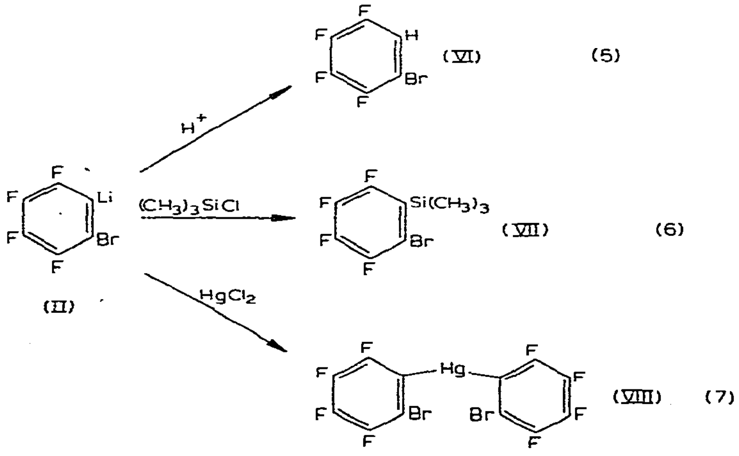


From previous studies[6,7,8,9] in benzyne chemistry*, one would expect that the anion of (II) would eliminate a bromide ion faster than fluoride in producing tetrafluorobenzyne (V) instead of bromotrifluorobenzyne (III). In our studies only one product (IV) was isolated, indicating a preference for fluoride ion elimination. These results could be rationalized by considering the following equilibria:



The reversibility of the elimination and addition of lithium halides to benzyne has been indicated by Wittig[7]. More recently Callender, Coe and Tatlow[10] have shown the addition of lithium salts (LiCl, LiBr, LiI) to tetrafluorobenzyne to be a general reaction. The major factor that could cause eqn. (3) to predominate may be attributed to the lesser solubility of lithium fluoride as compared to lithium bromide.

Intermediate (II) in most instances exhibited the general reactions of an organolithium reagent. In this manner a number of 2-bromotetrafluorobenzene derivatives



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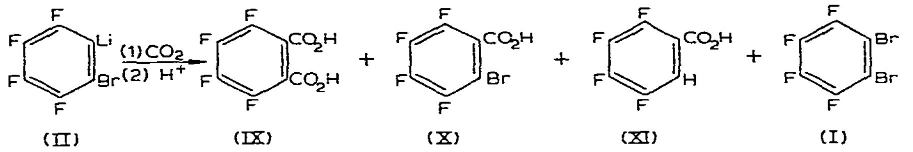
* For an excellent review on benzyne chemistry see ref. 6.

can be conveniently prepared*. The silane VII is easily hydrolyzed in a homogeneous ($THF-H_2O$) medium by 0.1 *N* sodium hydroxide solution to produce 1-bromo-2,3,4,5-tetrafluorobenzene. It is, however, stable (24 hours, room temperature) to 0.1 *N* sodium hydroxide solution in a heterogenous solvent system (diethyl ether/water).

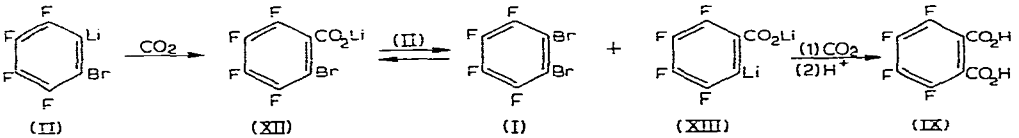
In the above three cited derivatizations of (II), the yields were high and no by-products were formed indicating the absence of secondary reactions. Carbonation of (II) however, proved to be an exception. Three acids were found: (IX), (X) and (XI)** in the ratio of 76:22:2 (peak area %). In addition 1,2-dibromo-3,4,5,6-tetrafluorobenzene (I) was also obtained. Since it has been shown that equivalent quantities of



(8)

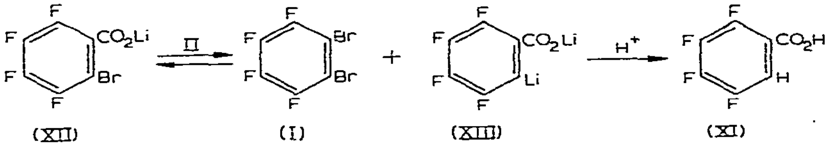
(I) and n-butyllithium yield no 1,2-dilithio-3,4,5,6-tetrafluorobenzene, it must be assumed that the diacid (IX) is produced by another means.

Our rationale for this anomaly can be explained by considering the following sequence of reactions:



(9)

To substantiate this reasoning, (XII) was synthesized independently and allowed to react with an equivalent of (II). Hydrolysis (instead of CO_2 treatment) of the mixture yielded products (I) and (XI), indicating the following reactions having taken place:



(10)

In addition to (I) and (XI), (VI) [from the hydrolysis of (II)] and (X) were also obtained, indicating that an equilibration*** of organolithium species occurs through metal–halogen interconversion.

The carbonation reactions described above were carried out by slowly bubbling carbon dioxide into (II). Under these conditions sufficient time was available for reactions described by eqn. (9), to take place. When the carbonation of (II) was performed by pouring it rapidly over crushed carbon dioxide, the yield of (X) was increased

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* (II) has been reported to react with sulfur[2] to yield bis(bromotetrafluorophenyl)sulfide and with titanium tetrachloride[3,5] to yield unstable (pentafluorophenyl)titanium compounds.

** No special precautions were taken to dry the carbon dioxide (Dry-Ice). Small amounts of residual water in the carbon dioxide would hydrolyze XIII to XI.

*** The nearly 50–50 ratio of products (see EXPERIMENTAL) indicates that if equilibrium had been reached its equilibration constant at these experimental conditions would be 1.

considerably: (IX) : (X) : (XI) = 11 : 82 : 7. Using this latter technique of carbonation decreased the time needed for reaction, eqn. (9), to take place and gave a lower yield of acid (IX).

Isolation and characterization of carboxylic acids through carbonation of organometallic intermediates has been generally used as an indication of an organometallic compound. If the rate of carbonation is slow compared to other possible competing reactions, care must be exercised in interpreting the composition of an organometallic compound through its carboxylic derivatives.

There is insufficient data at the present time to explain why carbonation of the organometallic (II) yielded a disubstituted (diacid) product while the other reactions of (II), hydrolysis, derivatization with trimethylchlorosilane and mercuric chloride yielded only monosubstituted products. Steric considerations alone cannot be the reason. A more reasonable explanation may involve the relative reactivities of the various equilibrated anions with the substrates. Kinetic studies determining equilibrium constants of various perfluoroanions and their subsequent reactions with substrates would be most helpful in interpreting our results. Such studies are in progress.

EXPERIMENTAL

All organometallic preparations were carried out under an atmosphere of dry, oxygen-free nitrogen. All melting points are uncorrected. Tetrahydrofuran was freshly distilled from sodium. VPC analyses were carried out on a F & M Model 500 gas chromatograph. A 6-ft. Apiezon L on Chromasorb W (60–80 mesh) column using helium carrier gas at about 60 cc/min was used. The temperature was programmed at 21°/min. The ^{19}F spectra were run on a Varian V-4300-2 D.P. Spectrometer at a 40 Mc/sec. Chemical shifts are reported in parts per million from trifluoroacetic acid. The ^{1}H NMR were run on a Varian A-60 spectrometer at 60.0 Mc/sec. Chemical shifts are reported in parts per million from TMS internal standard.

All polyfluorophenyl acids in this study were converted to their methyl esters with an ether solution of diazomethane. The methyl esters can be easily characterized by means of their retention times by VPC analysis.

The n-butyllithium used was commercially prepared in hexane solution by Foote Mineral Co., Exton, Pa.

2-Bromo-3,4,5,6-tetrafluorophenyllithium (II)

To a precooled (−70°), stirred solution of 1,2-dibromo-3,4,5,6-tetrafluorobenzene (0.05 mole, 15.4 g) in 150 ml of anhydrous diethyl ether was added n-butyllithium (0.05 mole, 33 ml of a hexane solution). The time of addition was 15 sec. One minute after addition an aliquot sample was removed, hydrolyzed, dried and examined by VPC. The organolithium solution was clear and light amber. Besides the solvent peak only two other peaks were found, butyl bromide and 2-bromo-3,4,5,6-tetrafluorobenzene. No 1,2-dibromo-3,4,5,6-tetrafluorobenzene was found. The solution was stirred at −70° for 24 h. Another sample was removed and analyzed as above. There was no change in the chromatographic trace, indicating no decomposition of the organolithium compound.

The solution was warmed to −27° and kept at this temperature for 6 h.

Another sample withdrawn and analyzed showed no decomposition of the organolithium compound. The solution was then raised to a temperature of 0° (ice bath) and after 4 h at this temperature another sample was removed. The VPC analysis indicated (in addition to solvent) the presence of butyl bromide, a decreased peak for 2-bromo-3,4,5,6-tetrafluorobenzene and at least 14 other peaks of various areas. After an additional period of 4 h at 0° another sample was removed and analyzed. Only a trace amount of 2-bromo-3,4,5,6-tetrafluorobenzene was indicated with the same 14 peaks of greater intensity. It is conceivable that there are additional products of decomposition which are not eluted from the column.

1,2,3-*Trifluoro-4-bromo-5,8-epoxy-5,8-dihydronaphthalene* (*IV*)

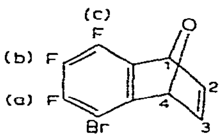
To a precooled (−70°), stirred solution of 1,2-dibromo-3,4,5,6-tetrafluorobenzene (0.05 mole, 15.4 g) in 100 ml of freshly distilled furan was added butyllithium (0.05 mole, 32.5 ml of a hexane solution). The time of addition was 9 min. After the mixture had been stirred for 30 min at −70°, a heavy white precipitate began to form. After 16 h of stirring at −70°, Color Test I[11] was still positive, indicating the presence of an organolithium compound. The reaction mixture was allowed to warm to room temperature. Color Test I was negative. The reaction mixture was hydrolyzed with 80 ml of 6 *N* HCl, phase separated and the organic layer dried over magnesium sulfate. VPC analysis of this solution indicated furan, butyl bromide, a trace of 2-bromo-3,4,5,6-tetrafluorobenzene and the product (IV), with a slight shoulder as an impurity. No 1,2,3,4-tetrafluoro-5,8-epoxy-5,8-dihydronaphthalene was indicated by VPC. Distillation of the solvent yielded 9.83 g (91 %) of crude product. Recrystallization from a minimum amount of ethanol gave a white, crystalline product, m.p. 61–63°. (Found: C, 42.89; H, 1.60; Br, 28.56; F, 20.17. $C_{10}H_4BrF_3O$ calcd.: C, 43.35; H, 1.46; Br, 28.84; F, 20.57 %.)

The aqueous layer (after hydrolysis) of the reaction indicated qualitatively the presence of fluoride ions and the absence of bromide ions.

The ^1H NMR (in $CDCl_3$ solution) and ^{19}F NMR (in C_2H_5OH solution) data are summarized in Table 1.

TABLE 1

^1H NMR (IN $CDCl_3$ SOLUTION) AND ^{19}F NMR (IN C_2H_5OH SOLUTION) DATA FOR 1,2,3-TRIFLUORO-4-BROMO-5,8-EPOXY-5,8-DIHYDRONAPHTHALENE



Assignment	*Chemical shift (ppm)*	*Rel. peak area*	*Spin coupling constants (cps)*
2, 3	7.1 (singlet[a])	2	~1
4	6.06 (broad)	1	
1	5.85 (broad)	1	
a	+54.5 (multiplet)	1	$J(F_a\text{–}F_b) = 21$ $J(F_a\text{–}F_c) = 4.5$
c	+63.4 (multiplet)	1	$J(F_b\text{–}F_c) = 16.5$ $J(F_c\text{–}H_1) = 2.5$
b	+82.0 (multiplet)	1	

[a] Singlet with fine structure, width at ½ height was 2.5 cps.

Trimethyl(2-bromo-3,4,5,6-tetrafluorophenyl)silane (VII)

To a precooled (−70°), stirred solution of 1,2-dibromo-3,4,5,6-tetrafluorobenzene (0.162 mole, 50.0 g) in 300 ml of anhydrous diethyl ether was added n-butyllithium (0.162 mole, 105 ml of a hexane solution). The time of addition was 12 min. After 30 min, trimethylchlorosilane (0.162 mole, 17.6 g) was added in 4 min. After 2 h at this temperature, Color Test I was positive, indicating the presence of an organolithium compound (II). The presence of (II) after this time indicates that at these temperatures the reaction (eqn. 6) is very slow. Stirring was continued for an additional 14 h at −70°. Color Test I was negative and therefore the reaction mixture was warmed to room temperature. The solution was filtered and the filtrate was aspirated to remove solvent and butyl bromide, leaving 48.7 g (99%) crude product. A VPC analysis of this material indicated only 2 products, ~2% butyl bromide and 98% product. This material then was distilled to yield 42.1 g (87%) of product (VII), b.p. 87–88° at 7 mm, n_D^{24} 1.4856. (Found: C, 35.81; H, 3.04; Br, 25.87; F, 25.45; Si, 8.88. $C_9H_9BrF_4Si$ calcd.: C, 35.89; H, 3.01; Br, 26.54; F, 25.23; Si, 9.33%.)

Bis(2-bromo-3,4,5,6-tetrafluorophenyl)mercury (VIII)

To a precooled (−70°), stirred solution of 1,2-dibromo-3,4,5,6-tetrafluorobenzene (0.10 mole, 30.8 g) in 300 ml of anhydrous diethyl ether was added n-butyllithium (0.1 mole, 65 ml of hexane solution). The time of addition was 10 min. After 30 min, anhydrous mercuric chloride (0.0475 mole, 12.9 g) was added. After 1¾ h, Color Test I was negative. Stirring at −70° was continued for an additional 19 h, after which time the reaction mixture was warmed to room temperature. The precipitate (product plus lithium chloride) was filtered and the filtrate aspirated to dryness to yield 20.1 g crude product. The filtered precipitate was extracted with benzene and the benzene aspirated to yield an additional 9.3 g crude product (total 94% crude yield). A sample of the crude product was sublimed at 1–2 mm, and recrystallized from carbon tetrachloride to yield an analytical sample, m.p. 160–162°. (Found: C, 21.61; Br, 24.07; F, 23.70; Hg, 29.95. $C_{12}Br_2F_8Hg$ calcd.: C, 21.95; Br, 24.34; F, 23.15; Hg, 30.55%.)

Reaction between (II) and lithium 2-bromo-3,4,5,6-tetrafluorobenzoate

To a mixture of lithium hydride (0.0073 mole, 0.0633 g) in 10 ml of anhydrous diethyl ether was added a solution of 2-bromo-3,4,5,6-tetrafluorobenzoic acid (0.0073 mole, 2.0 g) dissolved in 20 ml of anhydrous diethyl ether. After 2 h at room temperature, a sample was removed hydrolyzed, dried and treated with diazomethane. A VPC analysis indicated only one peak due to methyl 2-bromo-3,4,5,6-tetrafluorobenzoate. Meanwhile, a precooled (−70°), stirred solution of (II) was prepared from 1,2-dibromo-3,4,5,6-tetrafluorobenzene (0.0073 mole, 2.25 g) in 20 ml of anhydrous diethyl ether and n-butyllithium (0.0073 mole, 4.74 ml of a hexane solution). Fifteen min after the preparation of (II), VPC analysis indicated the presence of only n-butyl bromide and 2-bromo-3,4,5,6-tetrafluorobenzene. The lithium salt was then transferred to an addition funnel and added to (II) (at −70°) over a 3 min period. Stirring was continued for 75 min and the reaction was then hydrolyzed with 50 ml of 6 *N* HCl. The reaction was warmed to room temperature, phase separated and the organic layer extracted with base. VPC analysis of the non-acid portion indicated 2-bromo-3,4,5,6-tetrafluorobenzene (47 area %) and 1,2-dibromo-3,4,5,6-tetrafluorobenzene (53 area %). The basic layer was acidified with conc. HCl, extracted with diethyl ether and dried over magnesium sulfate. The dried ether layer was aspirated to dryness. A sample was treated with diazomethane and analyzed by VPC. Analysis indicated only 2 products, methyl 2-H-3,4,5,6-tetrafluorobenzoate (44 peak area %) and methyl 2-bromo-3,4,5,6-tetrafluorobenzoate (56 peak area %).

Carbonation of 2-*bromo*-3,4,5,6-*tetrafluorophenyllithium* (*II*)

To a precooled (−70°), stirred solution of 1,2-dibromo-3,4,5,6-tetrafluorobenzene (0.1 mole, 30.80 g) in 300 ml of anhydrous diethyl ether was added n-butyllithium (0.1 mole, 65 ml of a hexane solution). The time of addition was 7 min. After an additional 10 min, carbon dioxide was bubbled into the reaction mixture. One half hour later the cooling bath was removed and the reaction mixture warmed to room temperature with continued carbonation. The reaction was hydrolyzed with 200 ml of 6 *N* HCl, phase separated and the organic layer extracted with base. Aspiration of the dried non-acid fraction yielded 13.0 g of a light yellow liquid. A VPC analysis indicated besides butyl bromide, (VI) and (I) in a 7 : 65 ratio (peak area %).

The base-extracted layer from above was acidified with concentrated HCl, extracted with diethyl ether, dried over magnesium sulfate and aspirated to give 13.5 g of white crystals. A portion of this material was treated with diazomethane and analyzed by VPC. Three peaks appeared and were identified as (IX), (X) and (XI) in the ratio of 76 : 22 : 2 (peak area %).

The above experiment was repeated except that (II) was poured rapidly over crushed carbon dioxide (Dry Ice)/ether slurry. (I) was obtained in the non-acid fraction and the acid fraction contained (IX), (X) and (XI) in the ratio of 11 : 82 : 7 (peak area %).

ACKNOWLEDGEMENT

The authors wish to thank J. V. PUSTINGER, JR. and J. STROBEL of the Monsanto Research Corporation for the determination and interpretation of the NMR spectra reported.

SUMMARY

2-Bromo-3,4,5,6-tetrafluorophenyllithium has been prepared. Its stability, benzyne formation and reactions with water, trimethylchlorosilane and mercuric chloride have been studied. Anomalous reactions on carbonation of this organolithium reagent have been noted, and a reasonable explanation in terms of rates of carbonation is given.

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