Journal of Organometallic Chemistry, 215 (1981) 281—291
Elsevier Sequoia S.A., Lausanne — Printed in The Netherlands

1,3,5-TRISUBSTITUTED BENZENES

I. SYNTHESIS AND REACTIONS OF 3,5-DIBROMOPHENYLLITHIUM

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(Received January 5th, 1981)

Summary

An improved method for the synthesis of 3,5-dibromophenyllithium (I) has been developed. The reactions between I and various substrates leads to a variety of substituted compounds e.g. $(3,5\text{-}Br_2C_6H_3)_nX$; when $n = 1$, X = $\text{-}CO_2H$, -CHO, $\text{-}Si(CH_3)_2Cl$, $\text{-}C(O)C_3F_7$, $\text{-}C(O)CF_2(OCF_2CF_2)_3OC_2F_5$, $\text{-}C(O)CF(CF_3)OC_3F_7$, $\text{-}C(O)CF(CF_3)[OCF_2CF(CF_3)]_2OC_3F_7$, $\text{-}C(CF_3)_2OH$ and C_6F_5; when $n = 2$, X = $p\text{-}C_6F_4$; when $n = 3$, X = P. The thermal stability of I is also reported.

Introduction

Recently we have reported [1] an improved synthesis of *o*-bromophenyllithium and its reactions with a variety of substrates at —110°C. In an attempt to extend these studies to other bromoaryllithium intermediates, which may be temperature sensitive, we have investigated 3,5-dibromophenyllithium. This organolithium compound has previously been synthesized by Gilman, Langham and Moore [2] in a general study on metal—halogen exchange reactions with various haloaryl compounds. Further studies on I, however, have not been reported.

Discussion

Although numerous organometallic compounds may be synthesized, their utility as intermediates in the preparation of other compounds may be limited by their thermal instability. In the preparation of 3,5-dibromophenyllithium by the metal—halogen exchange reaction in diethyl ether solvent the final organo-

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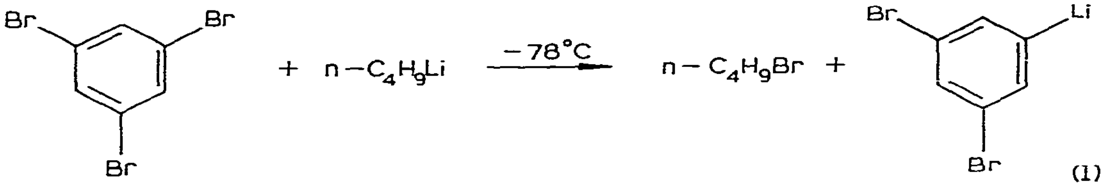
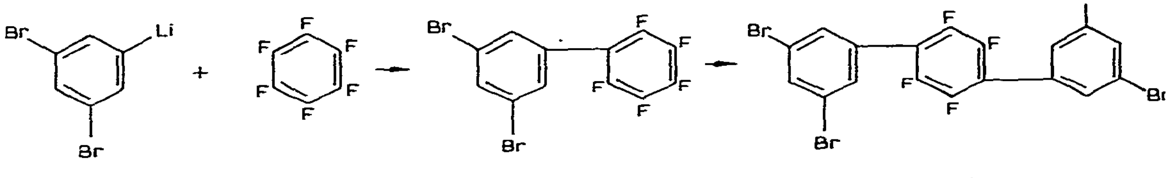


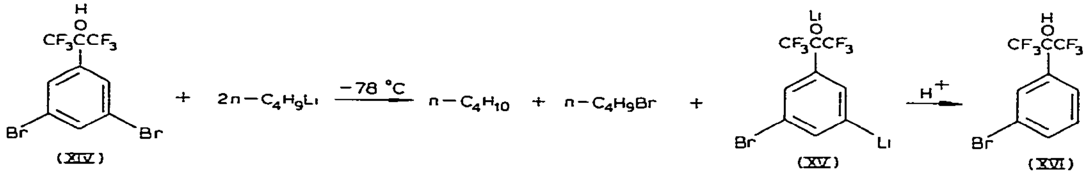
metallic compound I does not appear to have any chemical features, e.g. *ortho-bromo* substituent [1], which could lead to its thermal instability. It has been determined, however, that I is temperature-sensitive, and if precautions are not taken this can lead to lower yields of product as well as undesirable by-products. The mode of decomposition and products of reaction have not been investigated in detail as yet; however, its stability at various temperatures has been determined (see Experimental section). The products of decomposition are high melting intractable solids. The organolithium compound I can be conveniently prepared at —78° C in diethyl ether. The metal—halogen exchange is complete under these conditions and yields on hydrolysis the expected *meta*-dibromobenzene in nearly quantitative yield. An excess of n-C_4H_9Li over stoichiometric quantity replaces the second bromine to yield a small amount of bromodilithiobenzene. At this temperature I has sufficient stability and activity to react with numerous substrates of different functional character. In tetrahydrofuran (THF) as a solvent, however, the metal—halogen exchange reaction can proceed to a greater extent to yield multiple exchange. When stoichiometric amounts of 1,3,5-tribromobenzene and n-C_4H_9Li are allowed to react at —78° C, analysis of the hydrolyzed reaction indicated a mixture of C_6H_5Br (29%), *m*-$Br_2C_6H_4$ (25%), 1,3,5-$Br_3C_6H_3$ (28%), a trace of C_6H_6, and a number of other unidentified products probably from the subsequent reactions or decomposition of the various organolithium compounds. From the relative amounts of C_6H_5Br (29%), and *m*-$Br_2C_6H_4$ (25%), it would appear that in the THF solvent, the metal—halogen exchange reaction of the second bromine is as readily accomplished as the replacement of the first bromine.

Due to the thermal sensitivity of I, the reaction time and temperature of subsequent reactions with various substrates has a marked effect on products formed. With substrates as H_2O, CO_2, $(CH_3)_2NC(O)H$, $(CH_3)_2SiCl_2$, $R_fC(O)OC_2H_5$ [3], PCl_3 and $(CF_3)_2C{=}O$ high yields of products are obtained (see Table 1). It thus appears that I reacts at —78° C as a typical organolithium reagent with reactivity towards diverse substrates (See Scheme 1). As such it will be possible to prepare 3,5-dibromophenyl-substituted compounds of various types. With less reactive substrates, e.g. C_6F_6, which undergo nucleophilic reactions, under similar experimental conditions, the rate of reaction was extremely slow. Higher (—40° C) reaction temperatures and longer reaction times were required to effect any reaction. With C_6F_6 as a substrate, additional by-product formation was observed. Once the initial product XII was formed, it reacted faster than the unsubstituted C_6F_6 to produce the *para*-disubstituted product XI.



The *para*-orientation of XI was determined by ^{19}F NMR which showed only one type of fluorine substituent. The substitution by the 3,5-dibromophenyl group must activate the *para*-fluorine of XII towards further nucleophilic substitution by I.

The availability of these various 3,5-$Br_2C_6H_3X$ (where X = substituent from substrate) type compounds now provides the further possibility of metal—halogen exchange reactions on many of the compounds produced. Gilman and Arntzen have previously reported [4] metal—halogen exchange reactions with compounds such as BrC_6H_4OH and $BrC_6H_4CO_2H$ to yield LiC_6H_4OLi and $LiC_6H_4CO_2Li$, respectively. Utilizing 1,3,5-tribromobenzene and sequential metal—halogen exchange reactions, it is quite possible to use this synthesis method for the preparation of various BrC_6H_3XY type compounds (where X and Y are either similar or dissimilar). If, however, the substituent X is capable of reacting with n-C_4H_9Li, the metal—halogen exchange of the second bromine is competitive with X and a mixture of products may result. As an example, in the reaction between 3,5-$Br_2C_6H_3CO_2Li$ and n-C_4H_9Li a mixture of products was obtained. The principal product of this reaction was 3-$BrC_6H_4C(O)C_4H_9$, indicating that the n-C_4H_9Li reacted with both the carbonyl group as well as with one of the ring bromines through a metal—halogen exchange to yield on hydrolysis the protonated product 3-$BrC_6H_4C(O)C_4H_9$. With the monosubstituted compounds, 3,5-$Br_2C_6H_3X$, where X is not a reactive group toward n-C_4H_9Li, the second bromine can react via a metal—halogen exchange to yield a monolithio compound. Likewise, we have shown that when X contains a functional group, for example an -OH which can react with n-C_4H_9Li to form a lithium salt, two equivalents of n-C_4H_9Li are required to effect the second bromine metal—halogen exchange.



It is possible, beginning with 1,3,5-$Br_3C_6H_3$ to perform sequential metal—halogen exchange reactions where at least two different functional groups may be introduced without isolation of intermediate monosubstituted products.

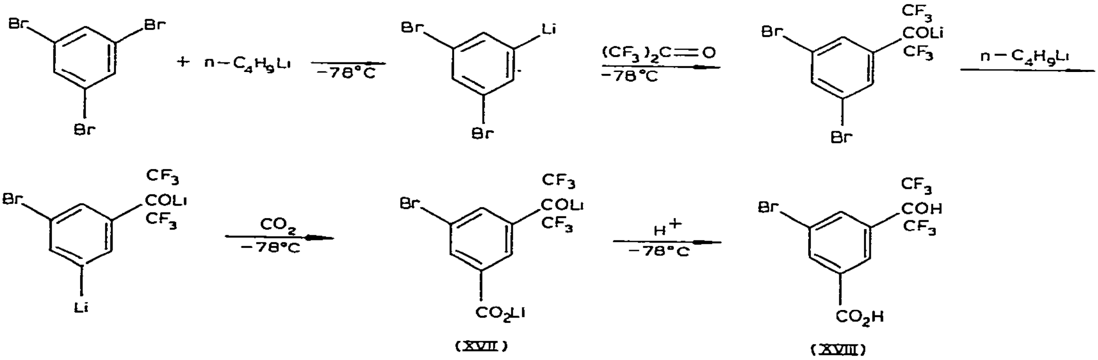


TABLE 1

PROPERTIES OF 3,5-DIBROMOPHENYL-SUBSTITUTED COMPOUNDS

Compound	B.P. (°C/mmHg)	M.p. (°C)	Yield[a] (%)	M.W. (Mass Spec.) Found (calcd.)	IR (cm^{-1})[b]	Analysis Found (calcd.) (%)			
						C	H	Br	Other
IV	—	90—92	86 (92)	262 (262) 264 (264) 266 (266)	1687[c] (C=O)	31.9 (31.9)	1.37 (1.53)	60.6 (60.6)	—
V	102/0.024	63—65	85 (95)	326 (326) 328 (328) 330 (330)	12.58 (Si—CH_3)[d] no Si—OH and Si—O—Si	31.4[e] (29.2)	3.04[e] (2.74)	48.1 (48.7)	10.7[f] (10.8)
VI	—	114—115	— (99)	598 (598) 600 (600) 602 (602) 604 (604) 606 (606)	1063[g] (Si—O—Si)	32.1 (31.9)	3.07 (3.01)	52.8 (53.1)	—
VII	61/0.05	—	93 (98)	430 (430) 432 (432) 434 (434)	1710[h] (C=O)	27.9 (27.8)	0.65 (0.70)	36.7 (37.0)	—
VIII	94/0.026	—	90 (98)	794 (794) 796 (796) 798 (798)	1725[h] (C=O)	24.4 (24.1)	0.38 (0.38)	20.3 (20.1)	—
IX	69/1.1	—	70 (83)	546 (546) 548 (548) 550 (550)	1710[h] (C=O)	26.0 (26.3)	0.53 (0.55)	29.0 (29.2)	—
X	79/0.008	—	80 (90)	878 (878) 880 (880) 882 (882)	1715[h] (C=O)	24.9 (24.6)	0.35 (0.34)	17.8 (18.2)	—

XI	—	271—272	39 (—)	614 (614) 616 (616) 618 (618) 620 (620) 622 (622)	1490—1550 ^{c}	35.0 (35.0)	0.80 (0.98)	51.3 (51.7)	—
XII	—	73—74	6 (—)	400 (400) 402 (402) 404 (404)	1470—1550 ^{c} (ArF)	36.1 (35.8)	0.36 (0.75)	39.5 (39.8)	—
XIII	—	146—148	83 ^{i}	730 (730) 732 (732) 734 (734) 736 (736) 738 (738) 740 (740) 742 (742)		29.3 (29.4)	1.12 (1.23)	65.0 (65.2)	4.34 ^{j} (4.21)
XIV	—	68—69	76 (94)	400 (400) 402 (402) 404 (404)	3500 (OH) ^{c}	26.9 (26.9)	0.91 (1.00)	39.8 (39.9)	—
XVIII	—	167—168	92 (95)	488 (488) 490 (490)	3500 (OH) ^{c} 1695 (C=O)	32.6 (32.7)	1.44 (1.37)	2.20 (2.18)	

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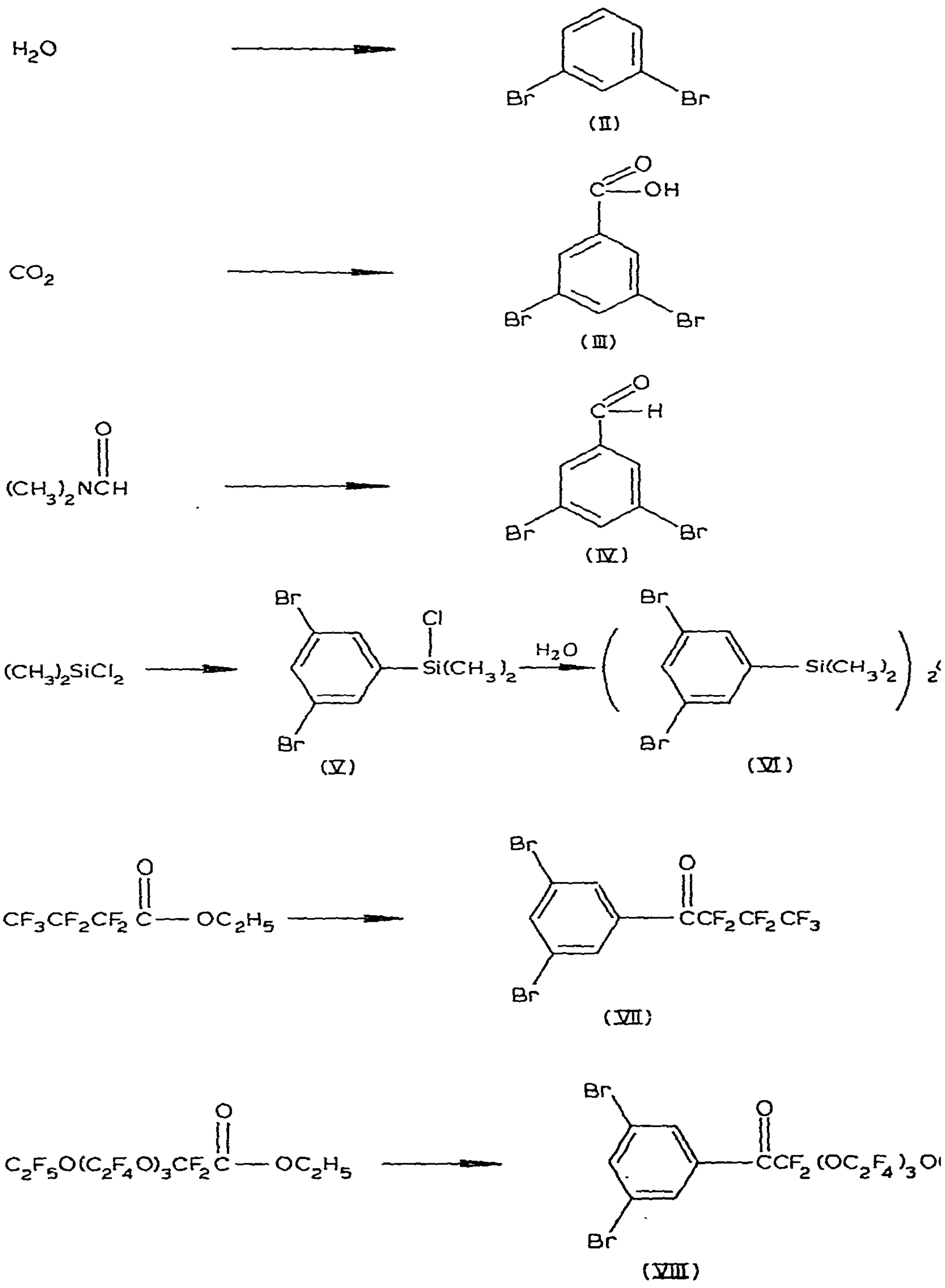
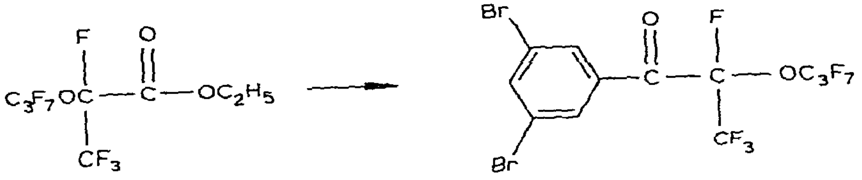
[a] Isolated values with GC area % values in parentheses. [b] All compounds are in general agreement with those observed in the spectrum of 1,3,5-trisubstituted benzene having absorption between 920—820 cm^{-1} [6]. [c] In KBr pellet. [d] In CCl_4 under nitrogen. [e] Difficulty was encountered in obtaining elemental analysis. [f] % of Cl, value was obtained by acid—base titration. [g] In CCl_4. [h] In liquid film. [i] Based on the amount of PCl_3 used. [j] % of P.

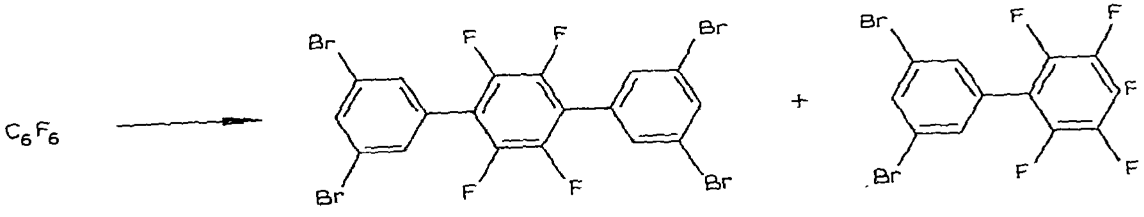
SCHEME 1

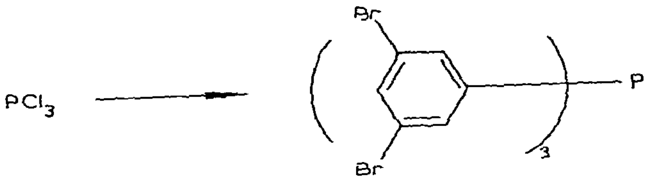
REACTION OF I WITH VARIOUS SUBSTRATES




(IX)


(X)


(XI) (XII)


(XIII)


(XIV)

The possibility of the sequential metal—halogen exchange reaction provides a synthesis route to a variety of polysubstituted 1,3,5-benzene compounds. Such studies which would involve the replacement of the third bromine on intermediates similar to XVII are now in progress and will be reported at a later date.

Experimental

General comments

All reactions were carried out in flame-dried glassware under an atmosphere of purified dry nitrogen. Tetrahydrofuran was dried by distillation from lithium aluminium hydride. Anhydrous diethyl ether (Mallinckrodt) was used without further purification. The yields reported were generally isolated yields except for those performed on small quantities where such yields were determined by gas chromatography (GC) using an internal standard. GC analyses were performed on an F&M Model 700 instrument using a 6 ft, 10% SE-30 on chromosorb W column. The GC/MS analyses were performed on a DuPont Model 21-490 mass spectrometer. All new principal products were characterized by elemental, mass spectral and infrared analysis. Most of the by-products of the reactions were characterized only by GC/MS analysis. Yields and elemental analytical data for all compounds are given in Table 1. n-Butyllithium in hexane was purchased from Alfa Division, Ventron Corp. All the temperatures reported are uncorrected.

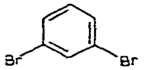
Preparation and stability of 3,5-dibromophenyllithium (I) in diethyl ether

Into a 250 ml four-necked flask, equipped with a stirrer, low temperature thermometer, a dropping funnel and a nitrogen gas inlet and maintained under a nitrogen atmosphere, was placed anhydrous diethyl ether (100 ml) and 1,3,5-tribromobenzene (3.15 g, 10.0 mmol). The contents were cooled to —78°C (2-propanol/dry ice bath) and n-C_4H_9Li (42.4 ml of 0.236 *M* in hexane solution, 10 mmol) was added at an even rate over 30 min while maintaining the internal temperature at —78°C. The solution was stirred at —78°C for an additional 30 min, an aliquot sample removed, hydrolyzed with 2 *N* HCl and analyzed by GC. Analysis indicated a 97% yield of 1,3-dibromobenzene (see Table 2).

The organolithium solution was allowed to warm up slowly during which time aliquot samples were removed periodically and analyzed by GC. The stability of

TABLE 2

STABILITY OF 3,5-DIBROMOPHENYLLITHIUM (I)

Reaction temperature (°C)	Time (h)	 (%)
—78	0.5	97
—78	19.5	91
—23	1	84
—23	3	78
—23	4.5	76
0	1	73
0	23	27

I is inferred by the amount of 1,3-dibromobenzene, the hydrolysis product of I, remaining in solution. See Table 2.

Preparation of I in THF

This preparation was performed in an identical manner to the one in diethyl ether. GC analysis, using an internal standard (n-octane), indicated a mixture of bromobenzene (29%), *m*-dibromobenzene (25%), 1,3,5-tribromobenzene (28%), a trace of benzene and an unidentified decomposition product.

Reaction of I with CO_2

A diethyl ether (1250 ml) solution of I (300 mmol) at —78°C was poured into a precooled (—50°C) saturated CO_2/diethyl ether (600 ml) solution. After 2 h, the solvents were removed, the residue acidified with 2 *N* HCl, extracted with diethyl ether and the diethyl ether solution further extracted with dil. NaOH. On acidifying the aqueous NaOH solution with 2 *N* HCl, the 3,5-dibromobenzoic acid (76.8 g, 91% yield) precipitated. The m.p. at 218°—220°C (lit. [4] m.p. 214°—216°C) and IR spectrum were identical to that in literature [5].

Reaction of I with $(CH_3)_2NC(O)H$

To a diethyl ether solution of I (31.7 mmol) at —78°C was added frehly distilled $(CH_3)_2NC(O)H$ (6.65 g, 91.1 mmol). After stirring at —78°C for one hour, the reaction mixture was hydrolyzed with 2 *N* HCl solution (400 ml). The diethyl ether layer was dried over $MgSO_4$, analyzed by GC and the solvent removed. The yield of 3,5-dibromobenzaldehyde (IV), melting at 90—92°C after recrystallization from diethyl ether and hexane, was 86% (7.2 g). See Table 1.

Reaction of I with excess $(CH_3)_2SiCl_2$

To a diethyl ether solution of I (95.1 mmol) at —78°C was rapidly added freshly distilled $(CH_3)_2SiCl_2$ (25.0 g, 194 mmol). After the reaction mixture was stirred for 1.5 h at —78°C, it was allowed to warm to room temperature, filtered under nitrogen and concentrated. Distillation of the concentrated filtrate yielded 3,5-dibromodimethylchlorosilylbenzene (V). See Table 1.

A sample of V in diethyl ether was hydrolyzed with water and stirred at room temperature for 30 min. Hexane was added to the diethyl ether solution. On concentration, crude dixiloxane VI separated which was further recrystallized from a mixture of diethyl ether and hexane to yield pure VI. See Table 1.

Reaction of I with n-$C_3F_7C(O)OC_2H_5$

To a diethyl ether solution of I (196 mmol) at —78°C was added n-$C_3F_7C(O)OC_2H_5$ (52.3 g, 216 mmol) dropwise with stirring over 30 min. After stirring at —78°C for one h, the reaction mixture was hydrolyzed at —78°C with 1 *N* HCl (600 ml), phase separated, dried over $MgSO_4$, solvent removed and analyzed by GC. Distillation of the concentrated mixture yielded the ketone VII. See Table 1. The other fluoroketones VIII, IX and X were prepared under identical conditions.

Reaction of I with excess C_6F_6

To a diethyl ether solution of I (47.7 mmol) at —78°C was rapidly added a diethyl ether (15 ml) solution of C_6F_6 (13.9 g, 74.7 mmol). After stirring the mixture at —78°C for 10 min, an aliquot sample was removed, hydrolyzed and analyzed by GC. Since the reaction was extremely slow at —78°C (as evidenced by *m*-dibromobenzene presence, 98%) the solution was allowed to warm up from —78°C to —40°C over 15 min and stirred at —40°C. Aliquots were removed from the solution at the end of 0.5 h, 1.5 h, 2.5 h and 3.25 h, and the respective yields of *m*-dibromobenzene after hydrolysis were 38%, 15%, 8% and 8%. After the reaction mixture had been stirred for 3.5 h at —40°C, it was allowed to warm to —10°C and then hydrolyzed with 1 *N* HCl (600 ml). The solid was filtered. The filtrate was then phase separated, dried over $MgSO_4$ and concentrated. After concentration of the diethyl ether layer, additional solid precipitated and was filtered. The combined solids (7.5 g; m.p. 265—269°, 51%) were recrystallized from toluene to give 5.8 g (39%) of product XI. See Table 1. The diethyl ether filtrates from above were concentrated to yield a solid which was sublimed at 85°C/0.2 mmHg to give 1.2 g (6.3%) of product XII. See Table 1.

Reaction of I with PCl_3

To a diethyl ether solution of I (70.1 mmol) at —78°C was added freshly distilled PCl_3 (2.89 g, 21.0 mmol) in 10 ml of anhydrous diethyl ether dropwise with stirring over 20 min. After stirring at —78°C for 30 min, the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 1.5 h, the reaction mixture was hydrolyzed with 1 *N* HCl (600 ml), additional diethyl ether was added to dissolve the precipitated product and the diethyl ether solution was phase separated and dried over $MgSO_4$. The solvents were removed to almost dryness at reduced pressure. The residue was washed with methanol (4 × 30 ml), to yield the crude product (15.6 g). The crude product was recrystallized from a mixture of chloroform and hexane to yield 12.8 g (83%) of product XIII. See Table 1.

Reaction of I with $CF_3C(O)CF_3$

To a diethyl ether solution of I (100 mmol) at —78°C was rapidly added $CF_3C(O)CF_3$ (17.4 g, 105 mmol) as a precooled liquid. An immediate exotherm was noted, —78°C to —60°C. The reaction mixture was cooled to —78°C and stirred for an additional 1 h. The reaction mixture was hydrolyzed at —78°C with 2 *N* HCl (500 ml), phase separated and the diethyl ether layer was dried ($MgSO_4$). The solvent and low boiling components were removed on a rotary evaporator at ~80°C leaving a white solid and some residual brown liquid. The mixture was filtered and the crude solid subjected to sublimation. At 85°C/10 mmHg a white crystalline solid product XIV was obtained, 30.4 g (76%). See Table 1.

Synthesis of XVIII

To a diethyl ether solution of I (100 mmol) at —78°C was rapidly added $CF_3C(O)CF_3$ (17.4 g, 105 mmol) as a precooled liquid. After 40 min at —78°C, n-C_4H_9Li (43.5 ml of a 2.30 *M* in hexane solution, 100 mmol) was added at an even rate over a period of 20 min while maintaining the internal temperature at

—78°C. The solution was stirred at —78°C for an additional 40 min, an aliquot sample removed, hydrolyzed with 2 *N* HCl and analyzed by GC. Analysis indicated a 97% metal—halogen exchange with the second bromine, as indicated by the formation of *m*-$BrC_6H_4C(CF_3)_2OH$ (XVI) (mass spectral analysis). Into the remainder of the reaction mixture CO_2 was bubbled through for a period of 70 min. The reaction mixture at —78°C was then hydrolyzed with 6 *N* HCl (700 ml), and the diethyl ether layer was separated and dried ($MgSO_4$). The solvent was removed on a rotary evaporator at ~80°C leaving a mixture of solid and liquid. The mixture was filtered and the crude solid product was washed with hexane (2 X 10 ml) yielding the product XVIII, 33.7 g (92%). See Table 1.

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