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FLUORO-KETONES.

V REACTIONS OF ALKYL AND ARYLLITHIUM COMPOUNDS WITH PERFLUOROALKYLETHER ESTERS*

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SUMMARY

n-Butyllithium and a variety of aryllithium compounds have been shown to react with a perfluoroalkylether ester ($R_fOR_fCO_2R$) at -78°C to produce perfluoroalkylether ketones. In the absence of competing reactions, which may be due to additional reactive groups on the ester, high yields of ketones can be prepared. Steric hindrance adjacent to the carbonyl group has an important effect on rates of reactions. Low reaction temperature (-78°C) is an important factor when secondary esters are used. At higher reaction temperatures (>-30°C), the secondary esters produce decreased yields of ketone due to the instability of the intermediate lithium salt of the hemiketal which decomposes to an aryl ester and a perfluorinated olefin.

INTRODUCTION

We have recently [1] reported the synthesis of fluorine containing ketones, $C_6H_5C(O)R_f$ (where R_f = CF_3, C_2F_5, n-C_3F_7, i-C_3F_7, $C_3F_7OCF(CF_3)$ and $C_2F_5O(CF_2CF_2O)_nCF_2$ via the reaction between C_6H_5Li and a perfluoroester $R_fC(O)OR$. Experimental details have been determined which provide a synthesis procedure for the preparation of $C_6H_5C(O)R_f$ compounds in high yields. As an extension of that study, we are now reporting on the general applicability of that reaction to a variety of organolithium compounds with various perfluoroesters.

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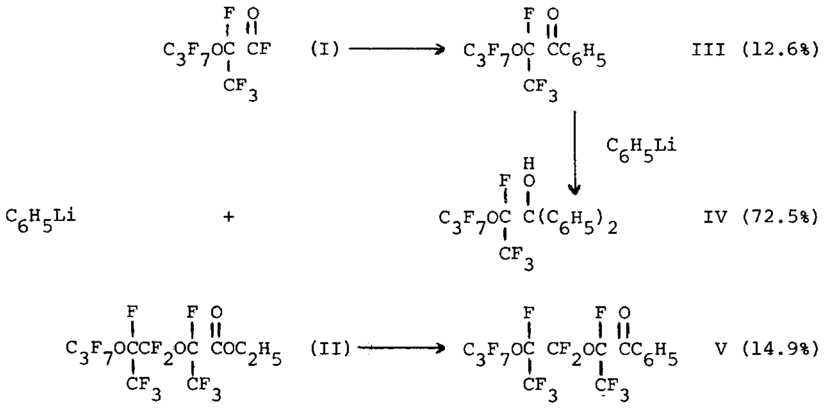
RESULTS AND DISCUSSION

Perfluoroesters, which may be prepared from perfluoroacid halides, have a distinct advantage over the perfluoroacid halides in reactions with organolithium compounds to produce perfluoroketones. A competition reaction between C_6H_5Li and a mixture of the ester II and the acid fluoride I in a 1:1:1 molar ratio at -78°C showed that the rate of reaction of the acid halide I is faster than that of the ester II. Since both I and II have the same steric constraints adjacent to the carbonyl group, the difference in the rates of reaction must be due to the nature of the functional group.

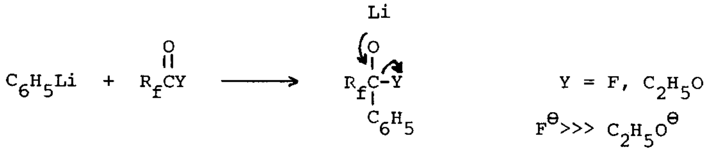


$$C_3F_7OCF(CF_3)COF \ \text{(I)} \longrightarrow C_3F_7OCF(CF_3)COC_6H_5 \ \text{III (12.6\%)} \xrightarrow{C_6H_5Li} C_3F_7OCF(CF_3)C(OH)(C_6H_5)_2 \ \text{IV (72.5\%)}$$

$$C_3F_7OCF(CF_3)CF_2OCF(CF_3)COC_2H_5 \ \text{(II)} \longrightarrow C_3F_7OCF(CF_3)CF_2OCF(CF_3)COC_6H_5 \ \text{V (14.9\%)}$$

(1)

The products of reaction derived from the acid fluoride I as compared to the ester II are in a ratio of 85:15 (G.C. area %). The ketone III which is readily formed at -78°C competes with I and II for the C_6H_5Li to form the alcohol IV.



$$C_6H_5Li + R_fC(O)Y \longrightarrow R_fC(OLi)(Y)C_6H_5$$

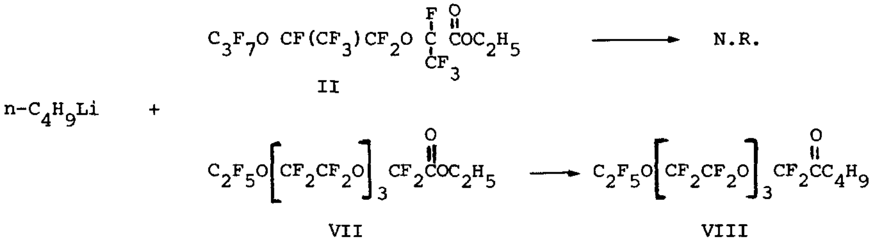
(VI)

(2)

The only product resulting from the ester II, however, is the ketone V. At -78°C the $F^{\ominus}$ is a much better leaving group than $C_2H_5O^{\ominus}$ group in the intermediate VI. When $Y = C_2H_5O$, VI is stable at -78°C and does not form the ketone V until much higher temperatures and therefore does not react with C_6H_5Li to form a tertiary alcohol [1].

Because of the greater thermal stability of the lithium salt of the hemiketal VI formed from the ester, this method of synthesis of ketones has a distinct advantage and a broad application in the synthesis of fluorine containing ketones. Since at -78°C the lithium salt of the hemiketal VI is stable, the order of addition of organolithium and ester is not important. Certain perfluoroesters, however, e.g., i-$C_3F_7CO_2R$ even at -78°C do not form a stable intermediate VI [1].

In this study, primary and secondary perfluoroalkylether esters were examined. The rate of reaction of the primary ester is much faster than the secondary ester apparently due to steric hindrance of the CF_3 group on the alpha carbon. A competition reaction between equimolar quantities of C_4H_9Li, II and VII, at -78°C, clearly indicated the faster rate of reaction of the primary ester.



$$n\text{-}C_4H_9Li \quad + \quad \begin{matrix} \underset{\text{II}}{C_3F_7O\;CF(CF_3)CF_2O\;\overset{F}{\underset{CF_3}{C}}\;\overset{O}{\overset{\|}{C}}OC_2H_5} & \longrightarrow & \text{N.R.} \\ \underset{\text{VII}}{C_2F_5O\left[CF_2CF_2O\right]_3CF_2\overset{O}{\overset{\|}{C}}OC_2H_5} & \longrightarrow & \underset{\text{VIII}}{C_2F_5O\left[CF_2CF_2O\right]_3CF_2\overset{O}{\overset{\|}{C}}C_4H_9} \end{matrix} \qquad (3)$$

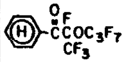
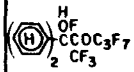
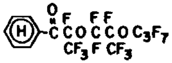
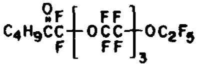
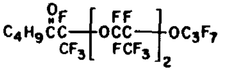
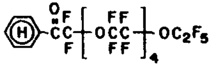
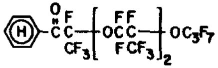
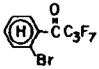
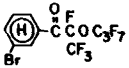
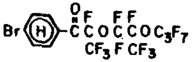
It was surprising to note that under a competitive reaction condition the primary ester VII reacted preferentially to the total exclusion of the secondary ester II. Under identical condition, except the exclusion of the primary ester VII, the secondary ester $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)CO_2C_2H_5$ (IX) reacted with n-C_4H_9Li to produce the ketone $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)C(O)C_4H_9$ (X) within a few minutes in 92% yield.

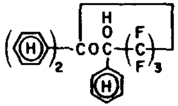
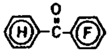
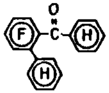
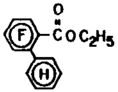
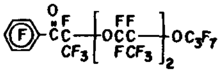
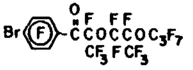
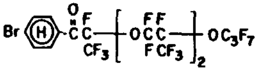
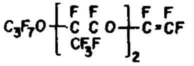
Following the low temperature procedure, various organolithium compounds were allowed to react with a variety of fluoroesters and the results are summarized in Table 1.

C_6H_5Li (Exp. 4,5) and (o, m, and p) BrC_6H_4Li (Exp. 6,7,8) give high yields of ketones XII, XIII, XIV, XV and XVI with no by-product formation. The reaction between C_6H_5Li and the diester XVII (Exp. 9) produced the diketone XVIII [2] in good yield, however, a competitive reaction produced the by-product XIX whose mode of formation has not been determined as yet. We have, however, found in some of our unpublished related efforts on synthesis of

TABLE 1

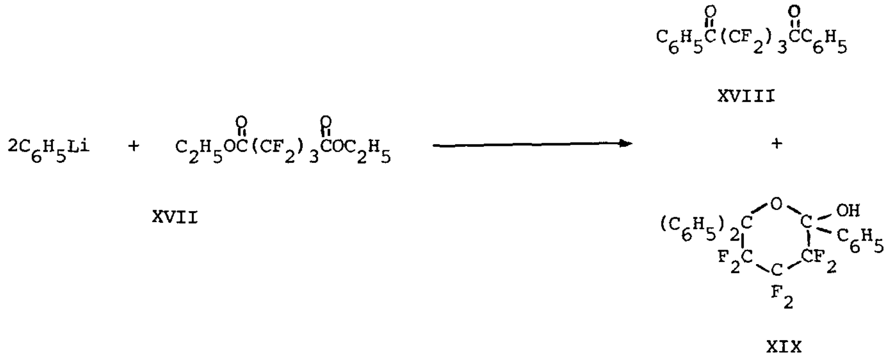
$RLi + R_fCO_2C_2H_5 \longrightarrow$ Ketone + by-products

Exp.	Compound	% Yield^a A	% Yield^a B	bp(mp) °C	MS cal'd / found	IR(cm^{-1})	Analysis cal'd / found C	Analysis cal'd / found H	Ref.
1	 (III)	12.6	---	80/18mm	390 / 390	1710(C=O)	--	--	4
	 (IV)(nc)	72.5	---	91/0.1mm	468 / 451(M-OH)	3600(OH)	46.17 / 46.34	2.37 / 2.06	---
	 (V)	14.9	---	114/5mm	556 / 556	1710(C=O)	--	--	4
2	 $C_4H_9\overset{O}{\overset{\|}{C}}\underset{F}{\overset{F}{C}}\left[O\underset{FF}{\overset{FF}{CC}}\right]_3OC_2F_5$ (VIII) (nc)	99	94	116/21mm	618 / 618	1760(C=O)	27.20 / 27.08	1.47 / 1.25	---
3	 $C_4H_9\overset{O}{\overset{\|}{C}}\underset{CF_3}{\overset{F}{C}}\left[O\underset{F\,CF_3}{\overset{F\,F}{CC}}\right]_2OC_3F_7$ (X) (nc)	92	77	107/15mm	702 / 702	1755(C=O)	27.37 / 26.91	1.13 / 1.29	---
4	 (XII)(nc)	92	70	89/0.47mm	754 / 754	1718(C=O)	28.66 / 28.51	0.67 / 0.68	---
5	 (XIII)	90	75.	76/1mm	690 / 690	1710(C=O)	29.90 / 29.80	0.70 / 0.62	4
6	 (XVI)	86	76	107/20mm	352,354 / 352,354	1735(C=O)			5
7	 (XV)	94	71	74/1.1mm	468,470 / 468,470	1710(C=O)	30.70 / 30.70	0.86 / 0.70	4
8	 (XIV)	92	83	91/1.1mm	634,636 / 634,636	1710(C=O)	28.37 / 28.43	0.63 / 0.69	4

9	 (XVIII)	85	61	(50-51)	$\frac{360}{360}$	1697,1710(C=O)	--	--	2
	 (XIX)(nc)	10	8	(145-146)	$\frac{438}{420(M-H_2O)}$	3580(OH)	$\frac{63.02}{63.40}$	$\frac{3.68}{3.53}$	--
10	 (XXI)	48	--	127/7.5mm	$\frac{272}{272}$	1690(C=O)	--	--	--
	 (XXII)(nc) b	18	--	144/0.4mm	$\frac{330}{330}$	1682(C=O)	$\frac{69.09}{68.90}$	$\frac{3.05}{2.93}$	--
	 (XXIII)(nc) b	16	--	143/7.5mm	$\frac{298}{298}$	1735(C=O)	$\frac{60.41}{60.50}$	$\frac{3.38}{3.07}$	--
11	 (XXIV)(nc)	84	60	71/1mm	$\frac{812}{812}$	1740(C=O)	$\frac{26.62}{26.70}$	$\frac{0}{0}$	--
12	 (XXV)	90	--	84/0.3mm	$\frac{706,708}{706,708}$	1750(C=O)	--	--	6
13	 (XXVII)(nc)	96	--	--	$\frac{800,802}{800,802}$		--	--	--
	 (XXIX)(nc)	--	47	110	$\frac{598}{598}$	1837(C=O)	$\frac{22.09}{21.70}$	$\frac{0}{0}$	--

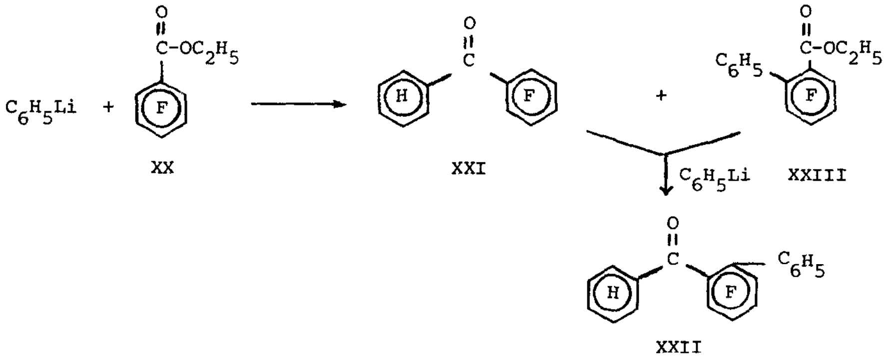
a. A=G.C. area ratio, B=isolated yield; b. ortho substitution determined by ^1H, ^{19}F and ^{13}C NMR analysis.

polyketones, that at a reaction temperature of -110°C, the secondary cyclic product resulting from the diester XVIII and an organolithium compound does not form.



(4)

The ester $C_6F_5CO_2C_2H_5$ (XX) has two reactive sites toward nucleophilic reaction, the aromatic fluorine and the carbonyl group. The reaction between C_6H_5Li and XX (Exp. 10) produced a mixture of products.

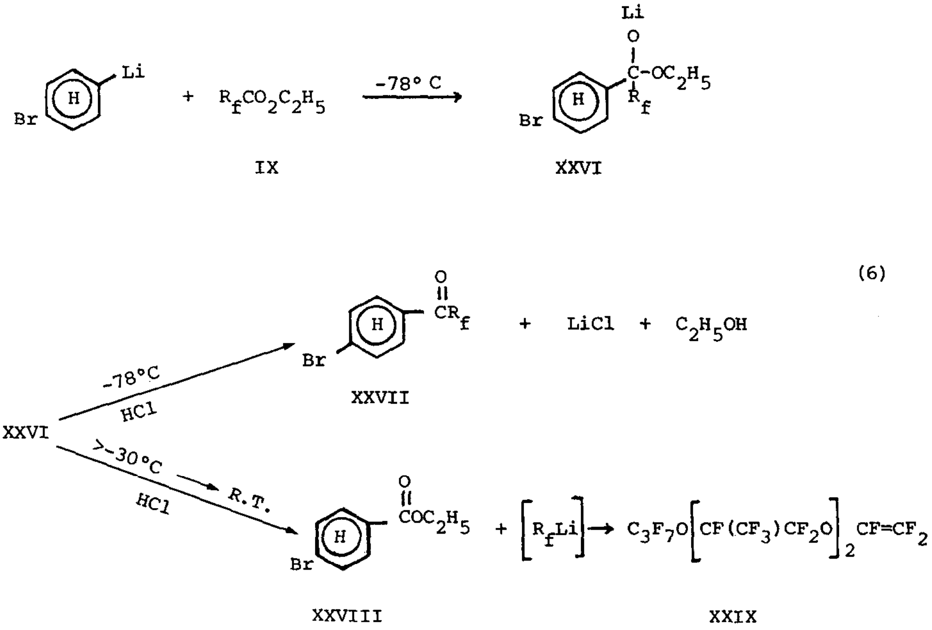


(5)

The ortho substitution by the C_6H_5 group in compounds XXII and XXIII was verified by ^{19}F NMR. It has been previously shown [3] that ortho substitution similarly takes place when C_6H_5MgBr was allowed to react with $C_6F_5CO_2CH_3$ (at 20°C) to yield XXI, the OCH_3 derivative of XXIII and $(C_6H_5)_2C_6F_5COH$. The formation of compound XXII was not noted.

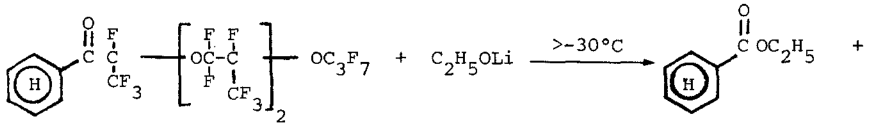
C_6F_5Li (Exp. 11) and p-BrC_6F_4Li (Exp. 12) compounds reacted with the $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)CO_2C_2H_5$ and $C_3F_7OCF(CF_3)CF_2OCF(CF_3)CO_2C_2H_5$ (II) to produce ketones XXIV and XXV respectively in high yield. Our previous [4] attempts to prepare XXV from the Grignard p-BrC_6F_4MgBr and $C_3F_7OCF(CF_3)CF_2OCF(CF_3)C(O)F$ were unsuccessful.

As indicated previously the success in preparing the ketones in improved yields is through low temperature (-78°C) stabilization of the intermediate lithium salt of the hemiketals. The intermediates derived from the secondary esters, however, are unstable at higher temperatures. This is shown (Exp. 13) by the reaction between p-BrC_6H_4Li and the ester $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)CO_2C_2H_5$ (IX).



(6)

At some temperature above -30°C the intermediate XXVI begins to decompose to XXVIII and R_fLi which is unstable and further decomposes by elimination of LiF to the olefin XXIX. Further support for this mechanism is provided by an independent experiment whereby C_2H_5OLi was added to the ketone XIII at -78°C. At this temperature on hydrolysis of the reaction mixture, the ketone XIII is quantitatively recovered. If, however, the reaction mixture is allowed to warm to room temperature the final products of the reaction are XXX and XXIX.



XIII XXX (7)

$$C_3F_7O\left[CF(CF_3)CF_2O\right]_2CF{=}CF_2$$

XXIX

It is quite apparent from the results of our present study that the reaction between a variety of organolithium compounds and perfluoroesters may provide a general procedure for the synthesis of fluorine containing mono- and polyketones.

EXPERIMENTAL

General Comments

All reactions were carried out in flame dried glassware under an atmosphere of purified dry nitrogen. Anhydrous diethyl ether (Mallinckrodt) was used without further purification. All melting points are uncorrected. All new compounds were characterized by NMR (^{19}F and ^{1}H), IR, mass spectral and combustion analysis. Gas chromatographic analysis (G.C.) were performed on a Hewlett-Packard Model 700 instrument using 6' or 12' stainless steel columns (1/4" d) packed with 10% SE-30 or Apiezon L on Chromosorb W. NMR spectra were obtained on an XL-100-15 spectrometer using TMS and $CFCl_3$ for references for ^{1}H and ^{19}F, respectively. Infrared spectra were obtained using a Perkin-Elmer Model 521 or 621 spectrophotometer as KBr wafers or neat liquids. Mass spectral analysis were performed on a Du Pont Model 21-490 mass spectrometer using a chemical ionization mode. The physical measurements and analyses of the various reactions are summarized in Table 1.

Competition Reaction Between C_6H_5Li, $C_3F_7OCF(CF_3)C(O)F$ (I) and $C_3F_7OCF(CF_3)CF_2OCF(CF_3)C(O)OC_2H_5$ (II)

To a diethyl ether (50ml) solution of I (3.32g; 10mmol) and II (5.24g; 10mmol) at -78°C was quickly added C_6H_5Li (6.25ml of 1.6M in diethyl ether-benzene, 10mmol). The white cloudy mixture turned a pale brown and the reaction temperature rose to -45°C. After 1 h, the reaction solution was hydrolyzed with 2N HCl (50ml) at -78°C. After warming to room temperature, the reaction was phase separated and the aqueous layer further extracted with diethyl ether (3 x 20ml). The combined organic layers were dried with $MgSO_4$ and analyzed by G.C. The G.C. area percent of the following products were indicated: $C_3F_7OCF(CF_3)C(O)C_6H_5$ III, 12.6%; $C_3F_7OCF(CF_3)C(C_6H_5)_2OH$ IV, 72.5%; $C_3F_7OCF(CF_3)CF_2OCF(CF_3)C(O)C_6H_5$ V, 14.9%.

Competition Reaction Between n-C_4H_9Li, $C_2F_5O[CF_2CF_2O]_3CF_2C(O)OC_2H_5$ (VII) and $C_3F_7OCF(CF_3)CF_2OCF(CF_3)C(O)OC_2H_5$ (II)

To a diethyl ether solution (440ml) of VII (5.00g; 8.25 mmol) and II (4.32g; 8.25 mmol) at -78°C was added n-C_4H_9Li (3.59ml of 2.3M in hexane, 8.25 mmol). A white cloudy mixture was obtained and the reaction temperature rose to -73°C. After 40 min, the reaction mixture was hydrolyzed with a precooled solution (-78°C) of conc. HCl (4 ml) in ethanol (12 ml) and the reaction temperature rose to -30°C. After 10 min, the reaction mixture was then poured into 2N HCl (500 ml), phase separated and aqueous layer further extracted with diethyl ether (3 x 100ml). The combined diethyl ether layers were dried with $MgSO_4$ and G.C. analysis indicated only one product, n-$C_4H_9C(O)CF_2[OCF_2CF_2]_3OC_2F_5$ (VIII).

The following is a general procedure for the reactions between various organolithium compounds and perfluoroesters. The results are shown in Table 1.

Synthesis of p-$BrC_6H_4C(O)(CF_3)CFOCF_2(CF_3)CFOC_3F_7$ (XIV)

To a diethyl ether (500 ml) solution of 1,4-$Br_2C_6H_4$ (49.5g; 0.21 mol) at -78°C was added n-C_4H_9Li (86.8 ml of 2.42M in hexane, 0.21 mol) over 2 h during which the colorless solution turned a cloudy pale yellow and the reaction temperature rose to -73°C. To this mixture $C_3F_7OCF(CF_3)CF_2OCF(CF_3)C(O)OC_2H_5$ (11.0g; 0.21 mol) was slowly added at -78°C during 1 h. A pale yellow solution was obtained and the reaction temperature rose to -75°C. After 1 h the reaction mixture at -78°C was hydrolyzed by 2N HCl (500 ml). After warming to room temperature, the mixture was phase separated and the aqueous layer further extracted with diethyl ether (3 x 100ml). The combined organic layers were dried with $MgSO_4$ and the diethyl ether and low boiling liquids were removed with a rotary evaporator at ∿40°C. The crude product was distilled to give the pure ketone XIV.

Reaction between C_6H_5Li and $C_2H_5OC(O)(CF_2)_3C(O)OC_2H_5$ (XVII)

To a diethyl ether (300 ml) solution of C_6H_5Li (168.8 ml of 1.6M in diethyl ether-benzene, 0.27 mol) at -78°C was slowly added the diester XVII (40.0g; 0.135 mol) during 25 min. The dark brown solution turned yellow and the reaction temperature rose to -70°C. After 2.5 h, the reaction mixture at -78°C was hydrolyzed with a 2N HCl (300 ml). The upper organic layer was separated and the lower aqueous layer extracted with diethyl ether (3 x 100 ml). The combined diethyl ether layers were dried with $MgSO_4$. G.C. analysis of this solution indicated two major products: $C_6H_5C(O)(CF_2)_3C(O)C_6H_5$ (XVIII) and XIX in an 85:10 ratio (G.C. area ratio). See Table 1. The structure of XIX was confirmed by ^1H and ^{19}F NMR(ppm): H, 7.4 (C_6H_5, 15H, 3 broad peaks) and 2.34 (OH, 1H, doublet): F, -106.6 (F in CF_2), -119.9 (2F in each of 2 CF_2), -121.5 (F in CF_2), -132.6 (F in CF_2), -138.5 (F in CF_2).

Reaction between C_6H_5Li and $C_6F_5C(O)OC_2H_5$ (XX)

To a diethyl ether (120 ml) solution of $C_6F_5C(O)OC_2H_5$ (9.78g; 40.8 mmol) was slowly added C_6H_5Li (38.1 ml of 1.07M diethyl ether, 40.8 mmol) at -78°C over 35 min. A pale yellow solution was obtained and the reaction temperature rose to -70°C. After 1 h at -78°C, the reaction was hydrolyzed with 2N HCl. The organic layer was phase separated and the aqueous layer was extracted with diethyl ether (3 x 50 ml). The combined diethyl ether solution was dried with $MgSO_4$ and the low boiling liquids were removed with a rotary evaporator at ca. 50°C. Analysis of the residue showed the following products in G.C. area percent: unreacted $C_6F_5C(O)OC_2H_5$ (XX), 16%; $C_6F_5C(O)C_6H_5$, XXI, 48%; o-$C_6H_5C_6F_4C(O)OC_2H_5$ (XXIII), 16%; o-$C_6H_5C_6F_4C(O)C_6H_5$ (XXII), 18%. Fractional distillation of the reaction mixture yielded sufficient quantities of materials for chracterization.

Reaction between p-BrC_6H_4Li and $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)C(O)OC_2H_5$ (IX) at -78°C to room temperature

To a diethyl ether (500 ml) solution of 1,4-$Br_2C_6H_4$ (11.8g; 50.0 mmol) at -78°C was slowly added n-C_4H_9Li (21.9 ml of 2.28M in hexane, 50.0 mmol) during 10 min. A white cloudy mixture was obtained and the reaction mixture temperature rose to -73°C. After 1 h, IX (34.5g; 50.0 mmol) was slowly added to the p-BrC_6H_4Li at -78°C over 15 min. A pale yellow solution was obtained and the reaction temperature rose to -74°C. The G.C. analysis of an aliquot sample which was hydrolyzed with 2N HCl, indicated $p\text{-}BrC_6H_4C(O)CF(CF_3)[OCF_2CF(CF_3)]_2OC_3F_7$ (XXVII) as the major product in 96 G.C. area percent. The compound was analyzed by GC/MS: calc'd. MW 800, 802; found MW 800,802. The remaining reaction mixture was allowed to warm to room temperature over a period of 30 min. After 17 h at room temperature the mixture was hydrolyzed with 2N HCl (300 ml), phase separated and the organic layer indicated two major products $C_3F_7O[CF(CF_3)CF_2O]_2CF{=}CF_2$ (XXIX) and $p\text{-}BrC_6H_4C(O)OC_2H_5$ (XXVIII). The compounds were isolated by fractional distillation to yield XXIX, 14.9g (47%) and XXVIII, 8.2g (71%). See Table 1.

Reaction between $LiOC_2H_5$ and $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)C(O)C_6H_5$ (XIII)

A mixture of $LiOC_2H_5$ (8.0 mmol) suspended in diethyl ether (30 ml) was added to XIII (5.78g; 8.00 mmol) at -78°C. The reaction mixture was stirred for 1.5 h and an aliquot sample removed, hydrolyzed with 2N HCl and analyzed by G.C. indicating only the starting ketone XIII. The reaction mixture was allowed to warm to room temperature. After 1.5 h at room temperature, the mixture was hydrolyzed with 2N HCl (50 ml) and the resulting upper organic layer was separated. The aqueous layer was extracted with additional diethyl ether (3 x 20 ml) and the combined diethyl ether solutions dried with $MgSO_4$. G.C. analysis indicated two major products $C_3F_7O[CF(CF_3)CF_2O]_2CF{=}CF_2$ (XXIX) and $C_6H_5C(O)OC_2H_5$ (XXX). Distillation yielded XXIX, 3.0g (63%) and XXX, 1.0g (83%).

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