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Regiospecific synthesis of aromatic compounds via organometallic intermediates.
Part 6. 1,3,5-perfluoroalkylether benzenes

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Abstract

1,3,5-Tribromobenzene can undergo a mono lithium–halogen exchange reaction to yield 3,5-$Br_2C_6H_3Li$ which can subsequently react with a perfluoroalkylether ester, $R_fOR_fC(O)OC_2H_5$, yielding the aryl ketone 3,5-$Br_2C_6H_3C(O)R_fOR_f$. A classical SF_4/HF reaction of this ketone yields the perfluoroalkylether benzene,3,5-$Br_2C_6H_3CF_2R_fOR_f$. This process can be repeated stepwise until all bromines are substituted, yielding the final product 1,3,5-$C_6H_3(CF_2R_fOR_f)_3$. The R_fOR_f was chosen as $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)$. Other perfluoroalkyl- and perfluoroalkyl-ether esters or other electrophiles can be chosen to react with the various organolithium intermediates.

Keywords: Regiospecific synthesis; Perfluoroalkylether benzenes; Mass spectrometry; IR spectroscopy

1. Introduction

Our previous studies on the regiospecific synthesis of aromatic compounds via aryllithium intermediates were concerned with 1,2-dibromobenzene [1,5], 1,4-dibromobenzene [3] and 1,3,5-tribromobenzene [2,4]. Mono phenyllithium intermediates of these polybromobenzenes were prepared by metal–halogen exchange reactions [6] and shown to react with a variety of compounds e.g. CO_2 [1–3,5], H_2O [1–3], $HC(O)N(CH_3)_2$ [1–3], $CH_3C(O)N(CH_3)_2$, [3], CH_3I [3], S [3], $(CH_3)_3SiCl$ [1,4], $(CH_3)_2SiClH$ [1], $(CH_3)_2SiCl_2$ [1,2], PCl_3 [2], $(CH_3)_3GeCl$ [4], $(CH_3)_3SnCl$ [4], C_6F_6 [1,2], $C_3F_7C(O)OC_2H_5$ [1,2], $C_2F_5O(C_2F_4O)_3CF_2C(O)OC_2H_5$ [2], $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)C(O)OC_2H_5$ [2], $(CF_3)_2C(O)$ [2], $CF_3C(O)CH_3$ [3,5]. Generally, high yields of mono-substituted (X) benzene compounds $XC_6H_{5-y}Br_y$ ($y = 1, 2$) were obtained.

These compounds, in turn, could be treated further with n-butyllithium to give substituted phenyllithium intermediates which reacted with electrophilic compounds to yield disubstituted products [2,3]. This process could be repeated until all available bromines were substituted.

In our continued studies using polybromobenzenes in a 'template-directed synthesis', we now report the synthesis of 1,3,5-tris(perfluoroalkylether)benzene [1,3,5-$(R_fOR_fCF_2)_3C_6H_3$, where $R_fOR_f = C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)$] by this technique.

2. Discussion

Recently, Chen, Chen and Eapen reported the synthesis of aromatic compounds having perfluoroalkyl (R_f) and perfluoroalkylether [$R_f'O(CF_2)_n$] substituents. They were made via copper-catalyzed cross-coupling reactions between mono-, di- and tri-bromoaromatic compounds and R_fI and $R_f'O(CF_2)_nI$ [7]. Generally, high yields of products were obtained with R_fI and with $R_f'O(CF_2)_nI$ where the oxygen was in position 5 or higher on —$O(CF_2)_nI$ unit ($n > 4$). When the oxygen was in the 3-position [—$O(CF_2)_2I$], no substituted products were obtained.

We now report our results on the preparation of 1,3,5-$(R_fOR_fCF_2)_3C_6H_3$ compounds by a multiple-step synthesis based on our previous studies [1–5]. The synthetic sequence is shown in Scheme 1. The metal–halogen exchange reactions, resulting in the formation of **I**, **IV** and **VII**, take place readily and give quantitative yields of the organolithium intermediates. This was determined by protonation of aliquot

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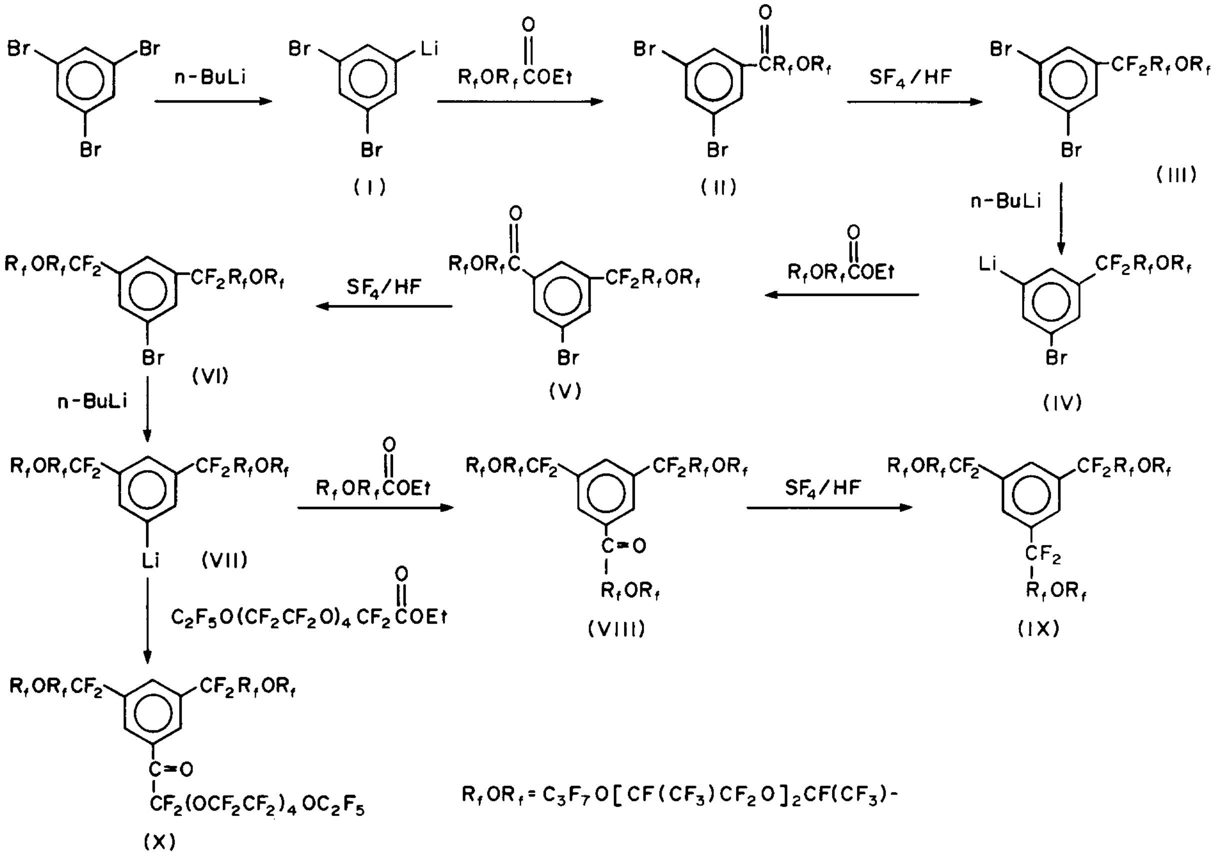

Scheme 1.

samples of the reaction mixtures by dilute HCl. GC analysis indicated complete disappearance of one bromine and the appearance of the protonated benzene derivative. The reactions between the organolithium intermediates and the perfluoroesters gave the ketones **II**, **V** and **VIII** which were isolated in 80%–90% yields. These were converted by SF_4/HF treatment to the perfluoroalkylether-substituted compounds **III**, **VI** and **IX**.

In this study, the three perfluoroalkylether groups were identical. The reaction sequence, however, allows for the introduction of a variety of substituents simply by varying the type of ester used in the reaction with the various substituted aryllithium intermediates. As an example, **VII** reacted with $C_2F_5O(CF_2CF_2O)_4CF_2C(O)OC_2H_5$ to give the ketone **X**.

Attempts to decrease the number of steps in the preparation of **IX** met with only partial success. Reaction between 1,3,5-tribromobenzene and 3 equiv. of n-butyllithium, followed by the addition of an excess of an ester, did not yield any of the desired product except the monosubstituted ketones (see Table 1, Exp. 2). From experiments 3 and 4, Table 1, it can be seen that **III** could be converted to the 3,5-dilithioperfluoroalkylether benzene in 72 GC area% yield to give, on hydrolysis with dilute HCl, the perfluoroalkylether benzene [8]. The product of the reaction between the dilithioperfluoroalkylether benzene and the ester $R_fOR_fC(O)OEt$ was the monosubstituted ketone, $3\text{-}(R_fOR_fCF_2)C_6H_4C(O)R_fOR_f$. These observations suggest that the lithium salts of the hemiketals $Li_2C_6H_3[C(OLi)(OEt)(C(O)R_f)]$ and $Li(R_fOR_fCF_2)C_6H_3[C(OLi)(OEt)(C(O)R_fOR_f)]$ may have very low solubility in the solvent.

The synthesis of **IX** as described above is a multistep procedure and may not be applicable to a practical large-scale synthesis of such compounds. It offers, however, the ability to substitute a variety of perfluoroalkyl and perfluoroalkylether substituents simply by varying the type of ester to be reacted with the organolithium intermediates **I**, **IV** and **VII**. Besides the esters, other electrophiles could react with the various organolithium intermediates as shown previously [1–5].

3. Experimental details

3.1. General comments

All reactions were carried out under an atmosphere of dry nitrogen at the specified reduced temperatures. The solvents diethyl ether and tetrahydrofuran were distilled from $LiAlH_4$ prior to use. Gas chromatographic analyses were performed

Table 1
Reactions of polybromobenzenes, n-butyllithium and dilute HCl or perfluoroalkylether ester

Exp. No.	Polybromobenzenes (PBB)	Molar ratio of PBB/n-C_4H_9Li	Electrophilic compounds	Solvent	Temp. (°C)	Products (GC area%) [a]
1	1,3,5-$Br_3C_6H_3$	1:3	Dilute HCl	Et_2O	−78	C_6H_6, BrC_6H_5, $Br_2C_6H_4$ [b]
2	1,3-5-$Br_3C_6H_3$	1:3	$R_f^2C(O)OEt$ [c]	Et_2O	−78	$R_f^2C(O)C_6H_5$ (2), [3-$R_f^2C(O)$]C_6H_4Br (16), 1,3-Br_2-5-[$R_f^2C(O)$]C_6H_3 (21) [d]
3	1,3-Br_2-5-($R_fOR_fCF_2$)C_6H_3 [e] (**III**)	1:2.2	Dilute HCl	Et_2O	−23	($R_fOR_fCF_2$)C_6H_5 (71), 3-($R_fOR_fCF_2$)C_6H_4Br (27)
4	**III**	1:3	Dilute HCl	Et_2O/THF (1:1)	−78	($R_fOR_fCF_2$)C_6H_5 (72), 3-($R_fOR_fCF_2$)C_6H_4Br (26)
5	**III**	1:3	$R_fOR_fC(O)OEt$ [e]	Et_2O	−65	[3-$R_fOR_fCF_2$]C_6H_4[$C(O)R_fOR_f$] (50) [3-$R_fOR_fCF_2$][5-$R_fOR_fC(O)$]C_6H_3Br (25) (**V**), ($R_fOR_fCF_2$)C_6H_5 (21)
6	**III**	1:3	$R_fOR_fC(O)OEt$ [e]	Et_2O/THF (1:1)	−65	[3-$R_fOR_fCF_2$]C_6H_4C[(O)R_fOR_f] (68), [3-$R_fOR_fCF_2$][5-$R_fOR_fC(O)$]C_6H_3Br (24) (**V**), ($R_fOR_fCF_2$)C_6H_5 (3)

[a] The products were identified by GC/MS only.

[b] Since the GC retention time of C_6H_6 was too close to the hexane (solvent for n-C_4H_9Li), the GC area% of all products could not be determined accurately.

[c] $R_f^2 = C_3F_7OCF(CF_3)$—

[d] Byproducts: $R_fC(O)C_4H_9$ (49%) and unknown (12%).

[e] $R_fOR_f = C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)$—

Table 2
Physical properties and analysis of products

Products	Boiling point (°C/mmHg)	Isolated yield (%) [GC area%]	IR (cm^{-1}) [a] (C=O)	MS (*m/z*)	Elemental analysis (calc./found)		
					%C	%H	%Br
II [b]	79/0.008	89 [90]	1715	878; 880; 882 (M^+)	24.60/24.90	0.34/0.35	18.2/17.8
III	126/0.30	83 [92]	–	900; 902; 904 (M^+)	23.97/23.96	0.33/0.13	17.7/17.9
V	128/0.024	81 [90]	1726	1466; 1468 (M^+)	24.54/24.60	0.20/0.15	5.45/5.34
VI	110/0.02	80 [90]	–	1488; 1490 (M^+)	24.18/24.19	0.20/0.26	5.37/5.35
VIII	158/0.02	55 [83]	1745	2055 $(M+1)^+$; 2035 $(M-F)^+$	24.55/24.67	0.15/0.14	–
IX	168/0.01	75 [86]	–	2076 (M^+)	24.29/24.05	0.15/0.09	–
X	170/0.30	60 [80]	1741	2086 (M^+)	24.18/24.52	0.14/0.13	–
XI [c]	180/0.02	8 [12]	3615 (—OH)	2087 $(M+1)^+$; 2067 $(M-F)^+$	24.75/24.85	0.34/0.31	–

[a] Neat liquid, capillary film between NaCl plates.

[b] Ref. [2].

[c] Byproduct from the synthesis of **VIII**.

on a Perkin-Elmer Sigma I chromatograph using a 6 ft stainless-steel column packed with 10% SE-30 on 80–100 mesh Supelcoport. The GC/MS analyses were obtained on a Finnegan 4021 mass spectrometer using either chemical ionization or electron impact mode. All new compounds were characterized by a combination of IR, GC/MS and elemental analyses (see Table 2). $R_fOR_f = C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)$—.

3.2. *Synthesis of 1,3-Br_2-5-$R_fOR_fC(O)$—C_6H_3 (II)*

Into a three-necked glass flask were placed diethyl ether (1800 ml) and 1,3,5-tribromobenzene (132.3 g, 0.42 mol).

The contents were cooled to −78 °C after which n-C_4H_9Li (201.0 ml of a 2.09 M solution in hexane, 0.42 mol) was slowly added over 1.5 h. After stirring the reaction for an additional 5 min, an aliquot sample removed, hydrolyzed with 1 N HCl and analyzed by GC. Analysis indicated a 93% yield of 1,3-dibromobenzene. To the above diethyl ether solution was added dropwise $R_fOR_fC(O)OC_2H_5$ (289.8 g, 0.42 mol) with stirring over 1.5 h. After stirring at −78 °C for an additional 30 min, the reaction mixture was hydrolyzed at −78 °C with 1 N HCl (2000 ml), phase-separated, dried over $MgSO_4$, solvent removed and analyzed by GC. The analysis indicated the major product **II** (90 GC area%). Distillation of the concentrated mixture yielded the ketone **II** (294.2 g, 80% yield) with a b.p. 75 °C/0.008 mmHg.

3.3. General procedure for SF_4/HF fluorination of ketones II, V and VIII

A 3 l stainless-steel autoclave was charged with **II** [2] (274.4 g, 0.312 mol) dissolved in $CFCl_2CF_2Cl$ (700 ml), cooled to −183 °C and evacuated. The autoclave was then charged with SF_4 (204.1 g, 1.89 mol) and HF (21.1 g, 1.1 mol) and warmed to 180 °C during a 4 h period. It was maintained at this temperature for an additional 48 h. The autoclave was cooled to room temperature, the gases vented to a storage cylinder and the vessel opened. The contents were poured over KF, filtered and the liquid passed through neutral alumina. The solvent was removed under vacuum leaving the crude product (281.1 g). Distillation under a vacuum gave **III** (see Table 2 for the fluorinated compounds **III**, **VI** and **IX** prepared by this procedure).

3.3.1. Synthesis of 3-($R_fOR_fCF_2$)-5-($F_fOR_fC(O)$)C_6H_3Br (V) (nc)

To a diethyl ether (1000 ml) and tetrahydrofuran (300 ml) solution of 1,3-Br_2-5-($R_fOR_fCF_2$)C_6H_3 (**III**) [2] (61.3 g, 68 mmol) was slowly added n-C_4H_9Li (28.2 ml of a 2.43 M solution in hexane, 68.5 mmol) at −78 °C over 18 min. After stirring the reaction for an additional 10 min, an aliquot sample was removed and hydrolyzed with dil. HCl. GC/MS analysis indicated complete conversion of **III** to the lithium intermediate **IV**. $R_fOR_fC(O)OC_2H_5$ (48.3 g, 70.0 mmol) was then added over 5 min while keeping the temperature at −78 °C. After 1 h of stirring, the mixture was hydrolyzed with a mixture of conc. HCl (10 ml) and THF (25 ml) at −78 °C. After an additional 5 min, the reaction mixture was poured into 2 N HCl (150 ml) at 0 °C, phase-separated and dried over $MgSO_4$. A GC/MS analysis indicated the major product **V** (90 GC area%) and the byproducts 3-($R_fOR_fCF_2$)C_6H_4Br (3 GC area%), 1-($R_fOR_fCF_2$)-3-R_fOR_f(CO)C_6H_4 (4 GC area%) and **III** (2 GC area%). Distillation yielded the product **V** (81.2 g, 81%). See Table 2.

3.3.2. Synthesizes of 1,3-($R_fOR_fCF_2$)$_2$-5-$R_fOR_fC(O)C_6H_3$ (VIII) (nc)

To a diethyl ether (300 ml) solution of n-C_4H_9Li (4.38 ml of a 2.3 M solution in hexane, 10.1 mmol) at −15 °C was added **VI** (5.0 g, 3.36 mmol) in diethyl ether (70 ml) over a period of 9 min. The reaction mixture was further cooled to −20 °C and $R_fOR_fC(O)OC_2H_5$ (6.81 g, 10.1 mmol) was added over a 2 min period while maintaining the internal temperature between −20 and −30 °C. The reaction mixture was stirred an additional 30 min. To this mixture, a precooled (−50 °C) solution of conc. HCl (10 ml) and ethanol (50 ml) was slowly added at −50 °C. After an additional 10 min, the reaction mixture was poured into 2 N HCl (500 ml), phase-separated and the organic layer dried ($MgSO_4$). A GC/MS analysis of the organic layer indicated the following: **VIII** (83 GC area%), 3,5-($R_fOR_fCF_2$)$_2C_6H_3C(OH)$-(OCH_3)R_fOR_f (**XI**) (12 GC area%) and 1,3-($R_fOR_fCF_2$)$_2C_6H_4$ (4 GC area%). Distillation yielded **VIII** (3.8 g, 55% yield) and **XI** (0.56 g, 8% yield). See Table 2.

3.4. Synthesis of 1,3-($R_fOR_fCF_2$)$_2$-5-[$C_2F_5O(C_2F_4O)_4CF_2C(O)$]$C_6H_3$ (X) (nc)

This compound was synthesized by a similar procedure to that described above for the preparation of **VIII**, except that the reaction between the organolithium **VII** and the ester was carried out at −15 °C for 1 h. A GC/MS analysis of the organic layer showed **X** (80 GC area%), **VI** (1 GC area%) and 1,3-($R_fOR_fCF_2$)$_2C_6H_4$ (19 GC area%). See Table 2.

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