FLUORAL HEMIACETAL, A NEW REAGENT FOR AROMATIC TRIFLUORO ALKYLATION

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SUMMARY

$\propto$ trifluoroalkylation of benzene was carried out in various
conditions (catalyst and solvent) by using the readily available fluoral
hemiacetal 1 as reagent. The good selectivity observed during the reaction
was explained by the HSAB concept.

INTRODUCTION

Fluorine compounds with CF_3 groups are of special interest and have
many applications in the pharmaceutical, dye and polymer industries
[1,2,3]. However, synthesis of such organic fluoro derivatives by methods
which are both efficient and selective is still a problem. Here we
describe trifluoroalkylation of benzene using fluoral hemiacetal.
This reaction is particularly useful, as a functional carbon chain with a
trifluoromethyl group can be added to an aromatic ring in a single step.
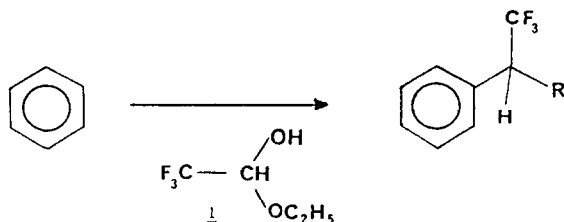
R_2 = OH : 2 ; OC_2H_5 : 3 ; Cl 4 ; C_6H_5 : 5

SCHEME 1. Trifluoromethyl alkylation using fluoral-hemiacetal 1

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The commercially available reagent 1 is stable under normal labo-
ratory conditions unlike the majority of aldehyde hemiacetals. Alcohol 2 ;
ether 3 ; chloride 4 and the diphenyl 5 derivatives were selectively
produced by modifying experimental conditions.

The different products obtained in the presence of various Lewis
acids, during the reaction between hemiacetal 1 and benzene, are given in
Table 1.

TABLE 1
Trifluoromethyl alkylation using fluoral hemiacetal in 1,2-
dichlorethane : Lewis acid effect

N^c	Lewis Acid*	2	3	4	5	Conversion yield %
1	AlCl$_3$	98 %	-	-		63
2	SbCl$_5$	85 %	11 %	-		55
3	FeCl$_3$	34 %	62 %	-		46
4	H$_2$SO$_4$	-	-	-	100 %**	70
5	AlCl$_3$	-	-	98 %	2 %	83

Relative yields were determined by G.C.
*
** Lewis Acid were added as 1 equivalent
   No other products were detected

It was possible to prepare each of the four trifluoro-methyl
derivatives by varying the type of catalyst used. The chloride derivative
4 was obtained when the reaction was carried out with 2 molecules of
aluminium chloride per molecule of substrate. This finding supports the
observation of LIOTTA [4] using chloral. Halogenoalkylation of benzene
with 1 was performed in 2 steps. Alcohol 3 was the primary product. A
second molecule of aluminium chloride was required for the production of
the chloride derivative 4.

It is important to note that the last reaction occurred at low temperatures (<20°C) whereas the classical transformation of alcohol in the presence of $AlCl_3$ takes place at 130°C [5]. It is highly likely that the second step involves the formation of the intermediary 6 which was gradually converted to chloride 4 (scheme 2).
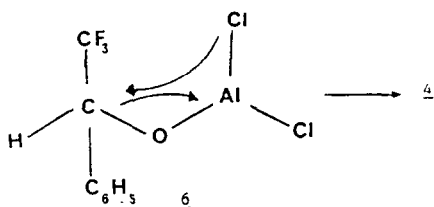
SCHEME 2. Formation of the chloride derivative 4

The latter hypothesis was supported by the fact that the carbinol 3 derivative was obtained instead of the chloride 4 derivative in a polar medium (nitromethane). This medium prevented formation of the intermediate compound 6 (Table 2 entries 6-9).

TABLE 2

Trifluoromethyl alkylation of benzene using fluoral hemiacetal : solvent effect

N°	Catalyst	Solvent	2	3	4	5	% Conversion Yield	ε *	μ *c.m.
1	$FeCl_3$ 1 eq. "	CH_3NO_2	34 %	65 %	-	-	79	35.87	11.88
2	"	$ClCH_2-CH_2Cl$	26 %	74 %	-	-	78	10.36	6.20
3	"	pet. ether	25 %	74 %	-	1 %	74		
4	"	CF_2Cl-CF_2Cl	13 %	87 %	-	-	45	2.4	
5	"	CS_2	11 %	87 %	-	-	64	2.64	
6	$AlCl_3$	CH_3NO_2	96.5 %	-	3 %	-	7	35.87	11.88
7	1 eq.	$ClCH_2-CH_2Cl$	98 %	-	1 %	-	63	30.36	6.20
8	$AlCl_3$	CH_3NO_2	86 %	-	4 %	1.5 %	75		
9	2 eq.	$ClCH_2-CH_2Cl$	-	-	98 %	2 %	71		

* ε Dielectric constant, μ Dipole moment (10)

1,1-Diphenyl-2,2,2-trifluoro ethane 5 was selectively prepared using a protic acid (H_2SO_4, Table 1, entry 4). The selectivity observed during preparation of 2 and 3, varied depending on catalyst and solvent. This can be largely explained using the HSAB concept.
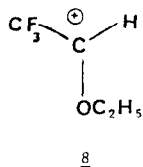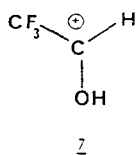
The type of intermediate required for the formation of carbinol 3 and/or ether 4 indicates that the surrounding substituent about the carbon atom produced two species (7, 8) of differing hardness. Species 7 was harder than 8, and the 7/8 ratio decreased with the hardness of the Lewis acid : $AlCl_3$>$SbCl_5$>$FeCl_3$ [6,7]. Use of a solvent of lower polarity. ranging from nitromethane to carbon disulfide, enhanced the Lewis acid/carbocation interaction and the effect of the softness of the Lewis acid i.e. the percentage of ether 3 versus alcohol 2 (Table 2, entries 1-5). Formation of intermediate 8, responsible for the production of ether 3 was favoured by the soft-soft interaction with a soft Lewis acid under slightly polar conditions (CS_2).

In conclusion, use of both the solvent effect and the HSAB concept permitted selective preparation of the four compounds 2, 3, 4, 5. Generalization of this method using different substrates, is presently under investigation in our laboratory.

EXPERIMENTAL

General procedure

All the reactions were carried out in dry vessel with anhydrous solvent under argon atmosphere. The Lewis acid catalyst was added in small portion

at a rate which maintains the desired temperature (10 mn). Study of the effects of Lewis acid and solvent using 0.27 g (3.5 mmol) of benzene and 0.5 g (3.5 mmol) of 2,2,2-trifluoro-1-ethoxy-ethanol in 5 ml of solvent was undertaken. The reaction was allowed to stand for 16 hours at room temperature. Suspensions were then poured onto crushed ice and extracted by CH_2Cl_2. After evaporation of the solvent, the mixture was titrated by G.C. on an SE 30 column at 180°C and using mesitol as internal standard. ^{1}HNMR spectra were determined in $CDCl_3$ with Perkin Elmer R32 (90 MHz) spectrometer ; signals are given in ppm from $SiMe_4$ as internal standard. IR spectra were recorded on a Perkin Elmer 457 spectrophotometer.

$\underline{2}$ Crude 2,2,2-trifluoro 1-phenyl-ethanol was distilled at 98°C/28mmHg : c.y. 53 %,
n_D^{22} 1.457, litt. 1.4568 [8];
^{1}HNMR ; 2.29 (s, 1H); 4.88 (q, 1H) ; 7.33 , (m, 5H).
IR (neat) ; OH 3390 cm^{-1} ; arom. 1480 cm^{-1}, 1450 cm^{-1} ; CF_3 1120 cm^{-1} ; 1165 cm^{-1}.

$\underline{3}$ Crude 2,2,2-trifluoro 1-phenyl-1-ethoxy-ethane was purified by liquid chromatography : SiO_2/hexane, ethylacetate. c.y. 70 %,
n_D^{25} 1.431 ;
^{1}HNMR ; 1.2 (t, 3H) ; 3.52 (q, 2H) ; 4.55 (q, 1H) ; 7.35 (m, 5H)
IR (neat) ; arom. 1400 cm^{-1}, 1490 cm^{-1} ; CF_3 1130 cm^{-1}, 1165 cm^{-1} ; C-O-C 1100 cm^{-1}, 900 cm^{-1}.

$\underline{4}$ Crude 2,2,2-trifluoro-1-phenyl-1-chloro-ethane was purified by liquid chromatography : SiO_2/heptane, ethylacetate. c.y. 82 % ;
^{1}HNMR $(CDCl_3)$; 5.1 (q, 1H) ; 7.42 (m, 5H).
IR (neat) ; arom. 1450 cm^{-1}, 1490 cm^{-1} ; CF_3 1120 cm^{-1}, 1160 cm^{-1} ; C-Cl 790 cm^{-1}.

5 Crude 2,2,2-trifluoro-1,1-diphenyl ethane was purified by liquid

chromatography ; aluminium oxide/ether. c.y. 70 %,

n_D^{25} : 1.520 ; litt. n_D^{22} : 1.523 [9];

^{1}HNMR ; 4.62 (q, 1H) ; 7.26 (m, H).

IR (neat) ; arom. 1450 cm^{-1}, 1490 cm^{-1} ; CF_3 1100 cm^{-1}, 1150 cm^{-1}.

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