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Catalytic fluorination of dichloromethylbenzene by HF in liquid phase. Preparation of fluorinated building blocks

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ABSTRACT

The selective fluorination by successive Cl/F exchanges of the dichloromethylbenzene, was studied in the presence of HF as the fluorinating agent. The influence of the presence of a catalyst or a basic solvent (such as dioxane, pyridine, tributylphosphate) in order to favour the fluorination was investigated. In mild conditions, (50 °C and after 1 h of reaction), the fluorination of the dichloromethylbenzene was observed and the polymerization reaction inhibited. The best results were obtained in the presence of the HF-dioxane system and antimony trifluoride as catalyst.

1. Introduction

The incorporation of fluorine, especially the $-CF_3$, $-CHF_2$ or $-CH_2F$ groups, into organic compound results in changes in the physical, chemical and biological properties [1–3]. These changes make them suitable for diverse applications in the areas mainly of agrochemistry and pharmaceuticals [4–6]. While a wide variety of methods have been developed for introducing trifluoromethyl groups into organic molecules [7–11], the most selective process is the fluorine–chlorine exchange used in industrial scale especially for the selective synthesis of fluorinated building blocks. The reaction between hydrofluoric acid and an organic halide can be carried out either in vapour phase or in liquid phase. Moreover in both cases, the presence of a Lewis acid or a metal oxide as catalyst increases the conversion of the chlorinated starting materials. The most catalyst commonly used in liquid phase fluorination reactions are antimony pentachloride ($SbCl_5$) or antimony mixed halides [12]. They are used in industrial scale reactions [13–15]. The catalytic processes offer a lot of advantages from classical chemistry. Indeed, the catalytic fluorination of chlorinated molecules (such as chlorinated hydrocarbon and aromatic) involving only Cl/F exchanges with HF as the fluorinating agent and a catalyst leads to high degree of fluorinated molecules and only to HCl as the by-product. Only a few examples of catalytic fluorination reactions have been reported in the academic literature.

Previous works [15] reported the fluorination of trichloromethoxy-benzene by liquid HF with various Lewis acids as catalysts. In this case, only Lewis acids with an oxidation degree of +V are efficient and $SbCl_5$ is the most powerful. The efficiency of these Lewis acids is due to their abilities to formnucleophilic complexes in the presence of HF. Indeed, the presence of few amount of the catalyst favored the last Cl/F exchange to produce fluoromethoxybenzene with only a stoichiometric amount of HF and a temperature of 50 °C. In the same way, the transformation of the bis-1,3-trichloromethylbenzene depends on the experimental conditions (temperature, amount of HF and the presence of a Lewis acid). In the presence of HF in excess, the hexafluorinated product was selectively observed whatever the conditions. The 1-trichloromethyl-3-trifluoromethylbenzene is selectively formed in the presence of low amount of HF alone and a temperature higher than 150 °C. Similar results were obtained in the presence of a Lewis acid at lower temperatures [16].

More recently, the selective trifluoromethylation of the corresponding chlorinated compounds was obtained by successive Cl/F exchanges under mild conditions with antimony pentachloride as catalyst and HF in stoichiometric amount as fluoride source. At 50 °C the conversion of trichloromethylbenzenesis total and the

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selectivity towards the trifluoromethylation is close to 100% with 2% of $SbCl_5$ and a stoichiometric amount of HF. On the other hand, the introduction of a basic solvent (dioxane, pyridine or tributylphosphate) allows the selective formation of the mono or difluorinated products depending on the HF-base amount which modulates the nucleophilicity of the fluoride source. The introduction of a catalyst with the HF-base system can increase either the conversion or the selectivity towards mono or difluorinated products. Depending on the fluorinating system, it could be possible to adapt the operating conditions in order to prepare selectively the mono, di or trifluorinated compounds with a good conversion of the starting materials [17]. Only, few works in the literature reported selective fluorination in the presence of a solvent [18–21] mainly HF-pyridine which is well known to be a good fluorinating agent.

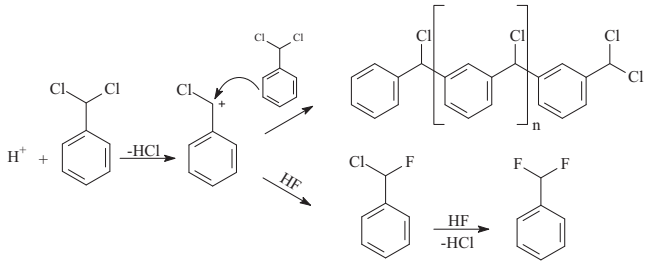
This paper deals with the fluorination of a $-CHCl_2$ group in the presence of HF-base systems (HF-pyridine, HF-dioxane and HF-tributylphosphate). Dichloromethylbenzene has been chosen as the model molecule. More particularly, the operating conditions (temperature, amount of HF, HF-base system) are studied in order to establish the best conditions to favour the fluorination reaction of the dichloromethylbenzene.

2. Results and discussion

2.1. Transformation of dichloromethylbenzene (DCMB) in the presence of the HF-base system

The transformation of dichloromethylbenzene was carried out for 1 h at 50 °C in the presence of various amount of HF and dioxane, pyridine or tributylphosphate as basic solvents. Various ratios between HF and the basic solvent (from 0 to 10) were studied. The conversion corresponds to the amount of the substrate transformed and the yield to the sum of the mono, difluorinated products.

Dichloromethylbenzene and trichloromethylbenzenes present different reactivities in the same operating conditions (50 °C). Indeed, when HF was used alone as the fluorinating agent, the transformation of the dichloromethylbenzene leads only to a solid into the autoclave corresponding only to the polymerization. Under these conditions, it was difficult to identify the products since they were not soluble in any solvent. However, considering the acidity of the medium, this could be corresponds to the polymerization of the substrate as reported Scheme 1. This reaction could be inhibited and the fluorination reaction favored when a basic solvent was added such as dioxane, pyridine or tributylphosphate. Indeed, in the presence of this kind of compounds, it could be possible to control the acidity of the reaction medium and to control the fluorination reaction as reported in a previous paper for the transformation of trichloromethylbenzenes [17]. When dioxane, pyridine or tributylphosphate was added, the polymerization reaction was inhibited. Indeed, in the presence dioxane corresponding to ratios between HF and dioxane of 2 and 3.5, the monofluorinated product is selectively observed. (Table 1). Beyond HF/dioxane ratio of 3.5, the polymerization reaction was again observed. This could correspond to the formation of bond between the oxygen atom and HF (as reported Scheme 2) which modulate the strength of the fluorine nucleophily. For HF/dioxane ratios higher than 4, free HF in the reaction medium is present. In the presence of HF/dioxane ratios of 2 or 4, the polymerization reaction disappeared, however only a fluorination yield of 2 or 4 was noticed. When, pyridine was used as solvent and whatever the HF:Pyridine ratios (from 3 to 10), only the fluorination reaction was also observed (Table 2). The fluorination yield increases with the HF/pyridine ratios. Indeed, an increase of the yield from 2.5 to 9 mol% is observed. In all cases, the monofluorination of the dichloromethylbenzene was the main product. As reported for the HF/dioxane system, an interaction between HF and the nitrogen atom explains the experimental results (Scheme 3). However, in the presence of the HF-tributylphosphate system, only the polymerization reaction was



Scheme 1. Transformation of dichloromethylbenzene in the presence of Broensted acid sites.

Table 1
Effect of the presence of dioxane in the transformation of dichloromethylbenzene (P_i = 10 bar, time = 1 h, T = 50 °C, substrate = 0.1 mol).

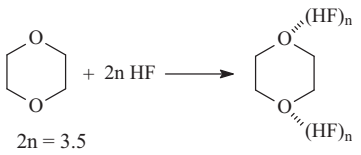
HF/diox	HF/Substrate molar ratio	Molar balance (%)	Conv. (mol%)[a]	Yield (mol%)[b]	Selectivity[c]		By-products (%mol)
					PhCHFCl (%)	$PhCHF_2$ (%)	
–	2	0	100		Polymerization		
2	2	92	14	2	100	0	4
3.5	4	73	33	4	100	0	2
7	8	0	100		Polymerization		

[a] Conversion: amount of substrate transformed.
[b] Yield: molar amount of fluorinated products (by-products excepted).
[c] Selectivity: amount of mono and difluorinated compounds.

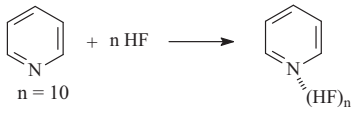
Table 2
Effect of the presence of pyridine in the transformation of dichloromethylbenzene (P_i = 10 bar, time = 1 h, T = 50 °C, substrate = 0.1 mol).

HF/pyridine	HF/ DCMB	Molar balance (%)	Conv. (mol%)[a]	Yield (mol%)[b]	Selectivity[c]		By-products (%mol)
					PhCHFCl (%)	$PhCHF_2$ (%)	
–	2	0	100		Polymerization		
3	2	86	14	2.5	60	40	1
6.5	4	98	14	8	75	25	4
10	6	93	20	9	67	33	4

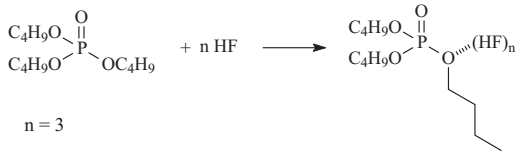
[a] Conversion: amount of substrate transformed.
[b] Yield: molar amount of fluorinated products (by-products excepted).
[c] Selectivity: amount of mono and difluorinated compounds.



Scheme 2. Formation of HF/dioxane complex.



Scheme 3. Formation of HF/pyridine complex.



Scheme 4. Formation of HF/tributylphosphate complex.

noticed whatever the HF/tributylphosphate ratio. As reported in the literature, pyridine was more basic than dioxane and tributylphosphate [22]. Consequently, the various complexes form between HF and dioxane, (Scheme 2) pyridine (Scheme 3) or tributylphosphate (Scheme 4) have not the same fluorination and acid properties.The fluorination yield could be increased from 4 to 19 mol% when the temperature rose from 50 to 150 °C (Table 3) in the presence of the HF-dioxane system. A change of the selectivity towards mono and di-fluorinated compounds was noticed. Indeed, the monofluorinated compound was the main product at 50 °C and the formation of the di-fluorinated was favored with the increase of the temperature. A change of conversion and yield of fluorination products was also obtained when the DCMB/dioxane ratio increased from 4 to 7 corresponding also to the formation mainly to the di-fluorinated compound (Table 4). The catalytic performances of various Lewis acid with various oxidation degrees were measured with the HF-dioxane fluorinating system for the transformation of dichloromethylbenzene. Lewis acid such as $TiCl_3$, TiF_3, $FeCl_3$ or $AlCl_3$, TiF_4, $TiCl_4$, SbF_5, $SbCl_5$, TaF_5, $NbCl_5$, NbF_5 $MoCl_5$ are evaluated. Under these experimental conditions, whatever the catalyst, only the polymerization reaction is observed. If the amount HF or the temperature were decreased in the presence of these catalytic systems, the conversion of dichloromethylbenzene was close to zero. An increase of the conversion of dichloromethylbenzene was found in the presence of SbF_3or BF_3 (Table 5). The fluorination yield increases from 18 to 48 mol% when the amount of SbF_3 added rises from 5 to 20%. In all cases, the selectivity towards the difluorinated compound was

Table 3
Effect of the temperature in the transformation of dichloromethylbenzene (P_i = 10 bar, time = 1 h, substrate = 0.1 mol, HF/dioxane = 4).

$T°$ (°C)	Molar balance (%)	Conv. (mol%)[a]	Yield (mol%)[b]	Selectivity[c]		By-products (%mol)
				PhCHFCl (%)	$PhCHF_2$ (%)	
50	73	33	4	100	0	2
100	90	35	18	33	67	7
150	67	67	19	26	74	15

[a] Conversion: amount of substrate transformed.
[b] Yield: molar amount of fluorinated products (by-products excepted).
[c] Selectivity: amount of mono and difluorinated compounds.

Table 4
Effect of the amount of dioxane in the transformation of dichloromethylbenzene (DCMB) (P_i = 10 bar, T = 50 °C, time = 1 h, substrate = 0.1 mol).

DCMB/dioxane	HF/dioxane	Molar balance (%)	Conv. (mol%)[a]	Yield (mol%)[b]	Selectivity[c]		By-products (%mol)
					PhCHFCl (%)	$PhCHF_2$ (%)	
0.3	3.5	73	33	4	100	0	2
1	7	75	36	7	29	71	4

[a] Conversion: amount of substrate transformed.
[b] Yield: molar amount of fluorinated products (by-products excepted).
[c] Selectivity: amount of mono and difluorinated compounds.

Table 5
Effect of the amount of catalyst (SbF_3or BF_3) on the transformation of dichloromethylbenzene (DCMB)(P_i = 10 bar, T = 100 °C, time = 1 h, substrate = 0.1 mol, HF/DCMB = 4, HF/dioxane = 3.5).

Catalyst (%mol)		Molar balance (%)	Conv. (mol%)[a]	Yield (mol%)[b]	Selectivity[c]		By-products (%mol)
					PhCHFCl (%)	$PhCHF_2$ (%)	
SbF_3	0	90	35	18	33	67	7
	5	93	48	31	29	71	10
	10	96	54	37	19	81	12
	20	99	64	48	12	88	15
BF_3	5	89	52	28	25	75	13
	10	0	100		Polymerization		

[a] Conversion: amount of substrate transformed.
[b] Yield: molar amount of fluorinated products (by-products excepted).
[c] Selectivity: amount of mono and difluorinated compounds.

favored. In the presence of BF_3, an increase of the conversion was also observed when 5 mol% was added. However, beyond this value, only the polymerization reaction was noticed. The transformation of dichloromethylbenzene which is very sensitive to the acidity of the reaction medium leads to only of the polymerization with the highest Lewis acidity. The best results for the fluorination dichloromethylbenzene are obtained in the presence of SbF_3, a moderate Lewis acid. In this case, the –C–Cl bond is activated by the presence of $SbF_3$and the fluorine source comes from the HF-dioxane system. When the Lewis acidity of catalyst is stronger, it could favored the dissociation of HF, the acidity of the reaction medium increases also and the reaction of polymerization of dichloromethylbenzene become the main reaction.

3. Conclusion

Based on our finding, we have determined the best conditions to favour the fluorination of the dichloromethylbenzene using HF-base system. Indeed, under these operating conditions, the polymerization reaction was totally inhibited by decreasing the acidity of the reaction medium. However, the fluorination yield is very low in the presence of HF and dioxane or pyridine. However it could be possible to increase this yield by increasing the temperature and/or adding a catalyst such as $SbF_3$to the reaction medium.

4. Experimental

4.1. Chemical products

All commercially available reagents were used without further purification. Hydrogen fluoride was purchased from Air Liquid; SbF_3 from VWR; dichloromethylbenzene, dioxane, pyridine and tributylphosphate from Aldrich.

4.2. General experimental procedure

All reactions were performed in a 100 mL stainless steel autoclave under an initial pressure of 10 bar. The temperature was regulated and controlled by means of a thermocouple placed in a thermometric well in the furnace wall. At the early stage of the experiment, the substrate and, depending on the experiment, the basic solvent and the catalyst were introduced in the autoclave. The difference in temperature between an HF cylinder warmed by means of a heating cord and the autoclave cooled in liquid nitrogen enabled the required amount of HF to be transferred to the reaction medium. The reaction took then place with continuous stirring, at the desired temperature (between 50 °C and 150 °C) and under autogene pressure. At the end of the reaction, the autoclave was cooled down and vented with dry dinitrogen in order to eliminate the HCl and the unreacted HF. The contents were quenched with 30 mL of water/dichloromethane mixture (50/50), using a 316 L stainless steel tank. After extraction with CH_2Cl_2, the organic phase was dried with $MgSO_4$ and analysed by GC. The fluorinated products and the chlorinated reactant were quantified by gas chromatography using bromobenzene as internal standard. The yield corresponds to the mol% of the various chlorinated compounds transformed into the corresponding fluorinated compounds. The difference between conversion and yield corresponds to non-identified by-products and the discrepancy of the experiment.

The chromatograph was a Varian 3380 equipped with 30 m VF-5ms (Varian) capillary column (inside diameter: 0.25 mm; film thickness: .1 μm) with a temperature program from 80 °C to 200 °C (5 °C/min) and then from 200 °C to 300 °C (10 °C/min).

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