Journal of Fluorine Chemistry 140 (2012) 43–48

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Direct trifluoro-methoxylation of aromatics with perfluoro-methyl-hypofluorite

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ARTICLE INFO

Article history:
Received 20 February 2012
Received in revised form 12 April 2012
Accepted 16 April 2012
Available online 24 April 2012

Keywords:
Trifluoromethylhypofluorite
Aromatic trifluoro-ethers
Radical trifluoro-methoxylation
DFT calculations

ABSTRACT

The reactivity of CF_3OF (FTM) has been widely studied especially in halogenated olefinic systems and its use in pharmaceutical synthesis as a mild radical and electrophilic fluorinating agent is well documented. On the other hand, the chemical behavior of the perfluoro-methyl-hypofluorite with aromatic substrates is much less studied. Up to now few and scattered data regarding its use as electrophilic fluorinating agent of variously substituted aromatic compounds are found in the literature. In this work the reactivity of CF_3OF with simple electron rich and electron poor aromatics (α,α,α-trifluoro-toluene, toluene, benzene, chloro-benzene, methoxybenzene) has been investigated. The possibility of selectively bind the trifluoro-methoxy group (via radical mechanism) or the fluorine atom (via electrophilic addition) by varying the reaction conditions has been explored. In particular we have observed that the trifluoro-methoxy free radical substitution can be the main synthetic pathway if the reaction is promoted by an independent and steady source of CF3O radical.

1. Introduction

Aromatic trifluoro-ethers are key-intermediates [1] in the production of bioactive molecules [2] since fluorine atom imparts desirable and valuable characteristics to drugs and pesticides [3,4]. The trifluoromethoxy group has increased utility as a substituent in bioactive compounds, but remains perhaps the least well understood fluorinated substituent currently in use [5–7]. Thus, several synthetic routes to prepare trifluoromethoxy aromatic derivatives have been developed over the last few years [8–22]. One of the most attractive option to synthesize this ether is the direct reaction between an aromatic compound and trifluoro-methyl-hypofluorite (FTM).

Trifluoro-methyl-hypofluorite is the simplest perfluoro-alkyl-hypofluorite [23,24] and is one of the most widely used source of trifluoro-methoxy group. It was first synthesized in 1948 by passing methanol or carbon monoxide and fluorine over silver difluoride at elevated temperatures [25–29]. Later, longer chain hypofluorites were prepared by treating the appropriate carbonyl compound with fluorine in the presence of dry cesium fluoride at low temperatures [26,27].

Generally, the reaction pathway between hypofluorites and unsaturated molecules is strongly dependent on the nature of the alkene. Electron-poor alkenes exhibit a radical reactivity with the formation of a trifluoromethoxylated ether [30–45] while electron-rich alkenes mostly undergo electrophilic fluorination as shown in Scheme 1.

The reactivity of CF_3OF (FTM) in the presence of aromatic molecules has already been studied and reported in the specialized literature [29,46]. It is recognized as a mild electrophilic fluorinating agent of aromatic substrates as shown in Scheme 2. However, this reaction is considered poorly convenient from the industrial point of view because it is "atomistically" inefficient since only one of the four fluorine atoms of the hypofluorite is used to fluorinate the aromatic substrate.

The radical reactivity of FTM has been widely studied in the presence of partially or fully halogenated olefinic systems and it is known from these studies that the trifluoromethoxylating chain is propagated by the CF_3O radical [46–49]. It was also found that by changing the experimental conditions it was possible to force the reaction path to follow preferentially one of the two possible pathways (radical *R* or electrophilic *E*) [50–52]. From our study the key intermediate that underlies the mechanism switch is the CF_3O radical because during the radical reaction between FTM and an electron-poor alkene the CF_3O radical is the carrier of the free radical chain reaction.

By exploiting this mechanism we have investigated the possibility to selectively bind, in one synthetic step, the

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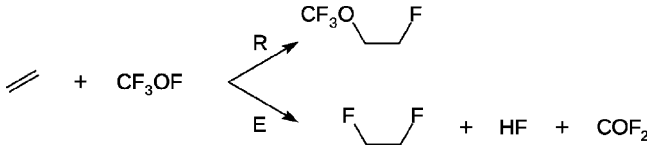
http://dx.doi.org/10.1016/j.jfluchem.2012.04.008



Scheme 1. Radical (*R*) and electrophilic (*E*) addition pathway of perfluoro-methyl-hypofluorite to alkenes.

trifluoro-methoxy group to a mono-substituted aromatic substrate (methoxybenzene, methylbenzene, benzene, chlorobenzene, α,α,α-trifluorotoluene) forming thus trifluoro-methoxy-aromatic products (CF_3O-Ar).

It has been shown that the reaction could proceed following a S.E.T. (single electron transfer) mechanism either producing the fluorinated or the trifluoromethoxylated moieties [27,50,53,54]. Moreover the production of mono-fluorinated aromatics relies on the fact that FTM is not highly polarized. Thus it has been proposed that the reaction will be facilitated because the trifluoromethoxy ion is an excellent leaving group that promptly decomposes to carbonyl-difluoride and fluoride ion [27,50,53,54].

In order to induce the production of CF_3O radicals through chemical initiation of FTM we have continuously added an electron-poor alkene like PMVE (trifluoromethyl-trifluorovinyl-ether, CF_3O–CF=CF_2) to the reaction mixture (radical addition *R*). The couple PMVE/TFM acts as in situ generator of trifluoromethoxy radicals thus resulting in a one-step synthesis of aromatic-trifluoro-ethers via radical addition as shown in Scheme 3. The aromatic substrates have been chosen amongst electron-rich (methoxybenzene, methylbenzene), benzene and electron poor (chlorobenzene, α,α,α-trifluorotoluene) moieties.

2. Material and methods

The main barrier that prevents a quick and in-depth study of hypofluorite chemistry is related to safety. Hypofluorites are very toxic and aggressive, thus any contact between these substances and the operator must be avoided. The reactors and the hypofluorite laboratory plant must be perfectly sealed and located in an efficiently ventilated dedicated area [37,55]. Organic hypofluorites should be regarded as potential explosives [56]. For safety reasons FTM was synthesized and used without any buffer storage. CF_3OF has been prepared in a PFR following a modified literature procedure by catalytic fluorination of carbonyl-difluoride on a fixed bed of porous metal fluorides [57–59]. This approach makes use of an understoichiometric amount of fluorine that helps avoiding the presence of fluorine traces in the FTM stream and hence the formation of byproducts.

Pure fluorine (99%) was bought from Solvay Fluor while pure PMVE (trifluoromethyl-trifluorovinyl-ether, CF_3O–CF=CF_2) was supplied by Solvay Specialty Polymers Italy. A 25 bar gaseous mixture of 3% PMVE in helium has been prepared and used for each experiment. Carbon monoxide (99.8%) used for the carbonyl-difluoride synthesis was purchased from Sapio.

To avoid potentially dangerous decomposition of FTM the pipelines of the continuous plant were cleaned and successively passivated with diluted fluorine. In addition the FTM gas stream was diluted with Helium in 1/5 (v/v) ratio. It is important to note that only few and scattered data about the toxicity of the trifluoromethoxylated aromatics are present in the literature. Due to this fact it is mandatory to handle these products with care.

2.1. Hypofluorite additions

2.1.1. Electrophilic addition E

The procedure consists of bubbling a stream of hypofluorite (5.5 NL/h: He = 80%, FTM = 18.5%, COF_2 = 1.5%) into a solution of the aromatic compounds maintained at the desired temperature (−30 °C; −80 °C) in a semi-batch method [57].

The solubility of the aromatic compounds was measured by carrying out a cloud-point measurement in selected solvents. All the aromatics tested (α,α,α-trifluoro-toluene, toluene, benzene, chloro-benzene, methoxybenzene) are soluble at concentrations between 4% and 5% in the chloro-fluoro-ether ($CF_3OCFClCF_2Cl$) used as reaction solvent.

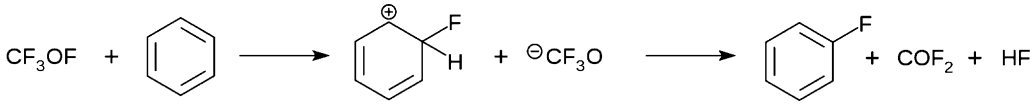
A cylinder containing 150 ml of a diluted (3%) solution of the aromatic substrate in 1,2-dichlorotrifluoroethyl-trifluoromethyl-ether ($CF_3OCFClCF_2Cl$) was prepared at room temperature. This solution was then poured in the 250 ml stainless steel stirred reactor, cooled at −40 °C and then stripped with helium for 15 min to eliminate the dissolved air since oxygen strongly interacts with radical based mechanisms.

Subsequently the hypofluorite stream was bubbled in the reactor kept at −40 °C under vigorous mechanical stirring. For one mole of aromatic substrate only 0.05–0.88 mol of hypofluorite were added, obtaining only a partial conversion of the aromatics.

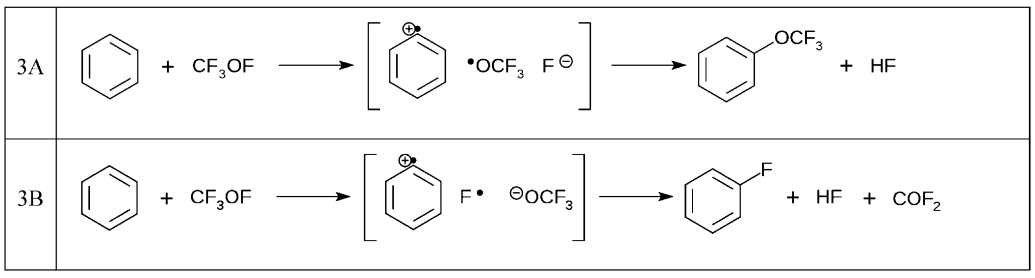
2.1.2. Radical addition R

The procedure for the radical addition is identical to the electrophilic methodology, but in addition it is characterized by the simultaneous feeding of FTM and PMVE as radical "promoter". For one mole of FTM less than 0.01 mol of PMVE were added during the reaction.

For both the methodologies the gaseous streams were constantly monitored by using an on-line GC-TCD (8 m PTFE Kel-F oil packed column) and a Thermo Nicolet 380 FT-IR furnished



Scheme 2. S.E.T./electrophilic fluorination of aromatics with perfluoro-methyl-hypofluorite (electrophilic pathway *E*).



Scheme 3. S.E.T./radical reaction between aromatics and perfluoro-methyl-hypofluorite [64,65].

with a custom PTFE gas-phase cell with CaF_2 windows, volume 8 cm^3, 10 cm optical path.

At the end of the addition reaction the unreacted FTM, the hydrogen fluoride and the dissolved carbonyl-difluoride were partially removed by bubbling in the reactor 5 NL/h of helium for about 3 h at −60 °C. After this stripping, the reactor cooling system was stopped and the reactor was finally allowed to reach room temperature. Stripping is a critical operation that serves to remove the unreacted FTM from the liquid products. Any traces of hypofluorite in the subsequent temperature ramp will likely result in losing selectivity and may result in a fast temperature rise.

The raw mixture was unloaded from the reactor into a 300 cm^3 cylinder and analyzed using a Thermo-Focus GC-TCD (Poraplot Q column), an Agilent GC–MS system 6850-5975C (Poraplot U column). A fractional distillation, at atmospheric pressure, using a common glass distiller was then performed. Three fractions were recovered: lightweights ($T_{head} < 40$ °C), solvent (T_{head} = 40–43 °C), and residue ($T_{boiler} > 50$ °C). All the fractions were analyzed. 98% of the total amount of aromatics was recovered in the residue together with small amounts of solvent. The lightweights fraction is mainly solvent with a purity higher than 98%.

MS trifluoromethoxy-anisole *m/z* (rel.int.): 50 $[CF_2]^+$ (24%), 69 $[CF_3]^+$ (100%), 75 $[C_6H_3]^+$ (16%), 92 $[C_6H_4O]^+$ (20%), 101 $[C_7H_2O]^+$ (40%), 103 $[C_7H_3O]^+$ (23%), 104.1 $[C_7H_4O]^+$ (38%), 123 $[C_7H_7O_2]^+$ (45%), 177 $[C_7H_4O_2F_3]^+$ (78%), 192 $[CH_3O–C_6H_4–OCF_3]^+$ (401%). MS trifluoromethoxy-toluene *m/z* (rel.int.) 50 $[CF_2]^+$ (23%), 69.2 $[CF_3]^+$ (100%), 90.2 $[C_7H_6]^+$ (48%), 91.2 $[C_7H_7]^+$ (112%), 104.2 $[C_7H_4O]^+$ (11%), 107.35 $[C_7H_7O]^+$ (16%), 156.25 $[C_8H_6OF_2]^+$ (70%), 174.35 $[C_8H_5OF_3]^+$ (14%), 175.25 $[C_8H_6OF_3]^+$ (98%), 176.35 $[CH_3–C_6H_4–OCF_3]^+$ (314%). MS trifluoromethoxy-benzene *m/z* (rel.int.): 50 $[CF_2]^+$ (16%), 69.05 $[CF_3]^+$ (100%), 77.06 $[C_6H_5]^+$ (20%), 93.03 $[C_6H_5O]^+$ (30%), 162.02 $[C_6H_5–OCF_3]^+$ (394%). MS chloro-trifluoromethoxy-benzene *m/z* (rel.int.) 50 $[CF_2]^+$ (17%), 69 $[CF_3]^+$ (100%), 73 $[C_6H]^+$ (34%), 74.1 $[C_6H_2]^+$ (17%), 75.1 $[C_6H_3]^+$ (42%), 92.1 $[C_6H_4O]^+$ (19%), 127 $[C_6H_4OCl]^+$ (50%), 196 $[Cl–C_6H_4–OCF_3]^+$ (502%). MS m-(trifluoromethoxy)-α,α,α-trifluorotoluene *m/z* (rel.int.) 69.2 $[CF_3]^+$ (100%), 75.2 $[C_6H_4]^+$ (12%), 113.2 $[C_8HO]^+$ (28%), 114.2 $[C_8H_2O]^+$ (34%), 133.2 $[C_8H_2OF]^+$ (55%), 145.25 $[C_7H_4F_3]^+$ (63%), 161.35 $[C_7H_4OF_3]^+$ (12%), 211.4 $[C_8H_4OF_5]^+$ (54%), 230.25 $[CF_3–C_6H_4–OCF_3]^+$ (292%).

2.2. Computational details

Computational studies were carried out on the substrate molecules under investigation. Minimum structures were obtained by density functional theory (DFT) calculations: the B3LYP hybrid functional [60–63] and the standard 6-311G** basis set were adopted. A vibrational analysis was performed on optimized geometries, where a lack of imaginary frequencies confirmed that they represent minimum-energy structures. Atomic charges for carbon atoms were calculated as the best fit to the molecular electrostatic potential (MEP) obtained at the B3LYP/6-311G** level of the theory. Gavezzotti radii were used for charges fitting. All calculations were performed with the GAMESS-US suite of programs [64,65].

3. Results

During the radical addition, *R*, the presence of unreacted hypofluorite in the off-gases has been observed. This fact is an indication that the reaction media is saturated with a large amount of FTM, as we have observed in a previous work [57]. By exploding the reaction mechanism it is possible to notice that the reaction with monosubstituted aromatics could proceed along with the production of six isomers: three possible mono-fluorinated isomers and three possible mono-(trifluoro-methoxylated) isomers. The reaction with highly activated substrates could also result, at high conversion, in the production of polyfluorinated aromatics. Due to the presence of a large number of isomers together with the solvent and the unreacted aromatic, the product separation, purification and identification was troublesome. The products were mainly qualitatively recognized using fragmentation data from GC–MS analyses. Isomer mixtures can be resolved during GC analyses. GC peak areas have been used to estimate product concentration and thus conversion by assuming a similar response factor for similar substances. The raw data collected from the GC analyses are summarized in Table 1.

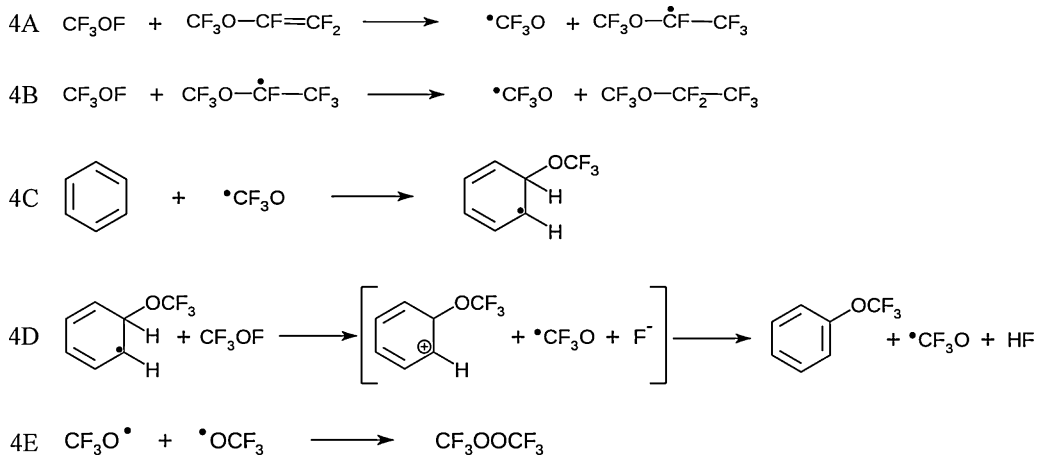
Traces of polyfluorinated aromatics have been found only at high conversion in tests involving electron-rich aromatics like methoxybenzene and toluene. In particular 2,5-difluoro-toluene and benzyl-fluoride have been found in trials involving toluene while in the tests with anisole the byproducts are mainly 2,4-difluoroanisole, 3,4-difluoroanisole, fluoro-methoxy-benzene and difluoro-methoxy-benzene.

4. Discussion

The different products distribution and thus the observed selectivity can be roughly explained by assuming a competition between the radical induced reaction (Scheme 4) and the electrophilic addition (Scheme 2). As it can be seen from Table 1, the electron density of the substrate plays an important role on the aromatic reactivity. The electron density on the aromatic ring depends on resonance and inductive effects created by the ring substituents. Values for the substrates used have been calculated by performing DFT simulations. Table 2 reports atomic charges for phenylic carbon atoms estimated as the best fit to the molecular

Table 1
Conversion, selectivity of the electrophilic (mono-fluorination), selectivity of the radical mono-(trifluoro-methoxylation) based on peak area for the electrophilic addition *E* and radical addition *R* evaluated by GC analyses. Runs 4 and 5 were both performed using methylbenzene with the radicalic activator. It was not possible to clearly identify the isomers in the analyses indicated with "*n*" thus the result has been omitted.

Run	Substrate	Addition	Aromatic conversion	Selectivity		Isomers distribution
				Ar–OCF_3	Ar–F	
1	Methoxybenzene	*E*	76%	11%	58%	Ortho and para isomers
2		*R*	77%	9%	66%	Ortho and para isomers
3	Methylbenzene	*E*	4%	50%	40%	n
4		*R*	16%	40%	10%	n
5		*R*	70%	44%	45%	n
6	Benzene	*E*	87%	38%	62%	
7		*R*	75%	54%	46%	
8	Chlorobenzene	*E*	33%	41%	41%	o/m/p: 7/1/8
9		*R*	44%	66%	23%	o/m/p: 5/1/5.5
10	α,α,α-Trifluorotoluene	*E*	0.21%	100%	0%	Meta isomer only
11		*R*	0.06%	100%	0%	Ortho and para isomers



Scheme 4. Radical mechanism for the addition of CF_3OF to aromatics in presence of $CF_3OCF{=}CF_2$ as free radical activator (radical addition *R*).

electrostatic potential (MEP) obtained on B3LYP/6-311G** optimized structures.

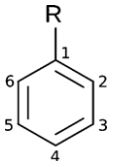
Highly electron-poor substrates (atomic charge > -0.09 [e^-]) like α,α,α-trifluorotoluene do not react significantly in the experimental conditions both in the electrophilic reaction or in the radical pathway, being CF_3O radical also electrophilic.

Conversely highly electron rich aromatics (atomic charge < -0.30 [e^-]) like methoxybenzene show preferentially an electrophilic behavior also at low temperatures as well as by inducing the radical reaction.

The reaction of FTM in the experimental conditions that favor the radical reactivity (low temperature and apolar solvent) proceeds in such a manner to obtain both fluorobenzene and trifluoromethoxybenzene derivatives. To account for the product distribution, the mechanism should be at the same time ionic and radicalic.

Depending on the substituent on the aromatic ring, the mechanism and hence products can be shifted towards the electrophilic or radical side but the product obtained is still made of a mixture containing either the trifluoro-methoxylated and fluoro substituted aromatics. The first explanation of this result, at least at high conversion, is in agreement with the mechanism proposed in the literature [49]. During the reaction, a highly polar product, hydrogen fluoride, is accumulating in the system. The presence of this compound could result in an ionic stabilization thus enhancing the amount of products derived from the electrophilic pathway (Scheme 2). The low polarity of the O–F bond in the FTM molecule may partly take in account for the ratio of fluorinated and trifluoromethoxylated aromatics in the electrophilic tests since both trifluoromethoxy and fluoride ions have the same probability to be a leaving group.

Table 2
Atomic charges [e^-] for aromatic carbon atoms estimated as the best fit to the MEP calculated at the B3LYP/6-311G** level. The last row contains an average atomic charge of the active sites indicated with 'X': position numbers 2, 4, 6 for the o,p orienting substituents (–OCH_3, –CH_3, –Cl) and positions 3 and 5 for the meta orienting groups (–CF_3). Average atomic charge of benzene takes in account all the equivalent six positions.



	Ar–OCH_3	Ar–CH_3	Ar–H	Ar–Cl	Ar–CF_3
1	0.52	0.35	-0.12^X	0.07	−0.07
2	-0.32^X	-0.28^X	-0.12^X	-0.09^X	−0.08
3	−0.06	−0.09	-0.11^X	−0.14	-0.08^X
4	-0.28^X	-0.18^X	-0.12^X	-0.12^X	−0.07
5	0.02	−0.07	-0.12^X	−0.14	-0.09^X
6	-0.40^X	-0.30^X	-0.11^X	-0.09^X	−0.08
Average	−0.33	−0.25	−0.12	−0.1	−0.08

In the presence of a radical promoter like PMVE, CF_3OF acts similarly as in the UV light activated reactions. The promoter induces the formation of CF_3O radical in steps 4A and 4B of Scheme 4.

The presence of a large excess of FTM in comparison with the small amount of PMVE used in the free radical activated trials assures that the alkyl radical derived from the olefin is completely depleted in step 4B thus resulting only in a volatile perfluorinated moiety ($CF_3O–CF_2–CF_3$) also recognized.

At the same time the ionic reaction in Scheme 2 is slowed down meanwhile hydrogen abstraction is a possible competitive mechanism, especially when the hydrogen is on the benzylic position [49].

In the experimental conditions adopted: low temperature, apolar solvent, electron poor reagent and fast induced initiation reaction, the free radical process, shown in steps 4C and 4D, is favored against the electrophilic addition.

Moreover, the key step 4D – rearomatization – is a very efficient propagation reaction generating the trifluoromethoxy compound and CF_3O radicals. Since the concentration of CF_3OF is high, all the electron rich carbon radicals will be easily oxidized to carbocations, which will undergo a facile rearomatization [66].

Due to the high excess of FTM and CF_3O radicals in the reaction media, the termination mechanism described in reaction 4E, consists in the coupling of the trifluoromethoxy radicals to form the perfluoro-di-methyl-peroxide (CF_3OOCF_3) already observed in similar experimental conditions [57].

Traces of polyfluorinated aromatics are visible only with electron-rich substrates at high conversion. The ratios 2-fluoroanisole/2,4-difluoroanisole and 2-fluoroanisole/3,4-difluoroanisole do not change between electrophylic and radicalic reactions. This finding suggests that the formation of the difluorinated products: 2,5-difluoro-toluene, 2,4-difluoroanisole, 3,4-difluoroanisole is a secondary reaction acting on the monofluorinated aromatics formed in the electrophilic reaction.

The free radical induced mechanism operates efficiently with toluene, benzene and chloro-benzene where the atomic charge of those aromatics is somewhere in the middle between highly activated and highly deactivated molecules.

In the reaction involving electron-poor compounds like α,α,α-trifluorotoluene the radical chain does not propagate, probably the reaction chain formed by steps 4C and 4D is not efficient enough to generate free radicals, therefore the amount of trifluoromethoxylated product is low and comparable to the amount of PMVE introduced. This behavior suggests that the governing reaction is the hydrogen abstraction and subsequent coupling with the CF_3O radical. In the case of electron-rich aromatics the experimental conditions adopted are not sufficient to suppress the electrophilic

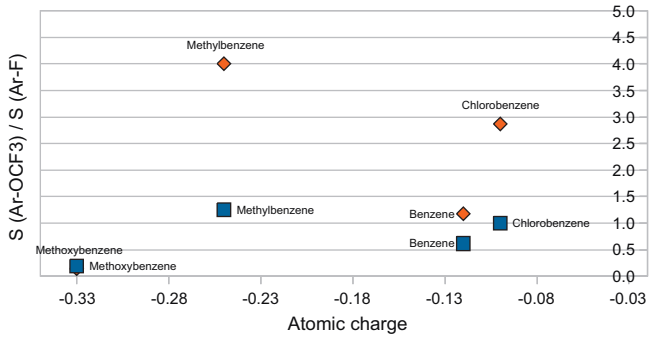


Fig. 1. A predictive approach combining the $(Ar–OCF_3)/(Ar–F)$ product ratio and the atomic charges obtained using DFT calculations. Red rhomb are referred to radical addition tests while blue square are referred to electrophilic tests. α,α,α-Trifluorotoluene has not been considered. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mechanism (or its relative S.E.T. reaction) with the production of the fluorinated aromatic as shown in Fig. 1 above.

The experimental results, together with the data coming from atomic charges (A.C.) estimated from DFT calculations in the interval $-0.30\ [e^-] < A.C. < -0.09\ [e^-]$, show that it is possible to increase the production of the trifluoromethoxylated moiety by adding PMVE to the reaction mixture. This calculated feasibility interval could be used to attempt predictions in the case of untested aromatics.

5. Conclusions

It has been shown that the reaction between an aromatic and FTM, at low temperature and in apolar solvent, gives products coming from either the radicalic or the electrophilic mechanism. It is possible to increase the radical contribution to the reaction by adding continuously a perfluoroolefin during the reaction: the olefin-induced radical mechanism increases the production of trifluoromethoxy radicals and hence the related aromatic ether. This is confirmed by the data coming from atomic charges estimated by DFT calculations, in the interval $-0.30\ [e^-] < A.C. < -0.09\ [e^-]$. The radical induced mechanism is more efficient with toluene, benzene and chloro-benzene where the atomic charge is somewhere in the middle between highly activated and highly deactivated molecules. The calculated feasibility interval could be used to attempt predictions in the case of untested aromatics. Inside this feasibility interval, the selectivity to the trifluoro-methoxylated product is higher when the conversion is low. A possible explanation of this conversion dependent behavior resides in the change of the solvent polarity during the reaction due to the buildup of hydrogen fluoride.

In the reaction involving electron-poor compounds like α,α,α-trifluorotoluene the trifluoromethoxylation is very difficult, indeed the radical chain cannot propagate thus resulting in a low amount of aromatic ether produced, similar to the amount of activator added. In the case of electron-rich compounds the experimental conditions adopted are not sufficient to overcome the electrophilic mechanism and the production of the fluorinated aromatic.

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