Organic Process Research & Development

ARTICLE

pubs.acs.org/OPRD

The Preparation of Desflurane by the Vapor-Phase Fluorination of Isoflurane

Hariharan Sivaramakrishnan, Abhay A. Upare, Damodharan Satagopan, and Owen R. Chambers*,§

Piramal Healthcare Research Centre, Piramal Healthcare India Limited, 1-Nirlon Complex, Off Western Express Highway, Goregaon (East), Mumbai −400 063, India

ABSTRACT: There are several known processes for manufacturing the commercially important anaesthetic desflurane ($CF_3CHFOCHF_2$) by the catalyzed reaction of commercially available isoflurane ($CF_3CHClOCHF_2$) with hydrogen fluoride. The present available methods have the disadvantage of high catalyst usage, with consequent environmental problems, or of having to trade off low conversion against low selectivity. An alternative catalyst system was therefore sought that would avoid these problems, but would still give the benefits of a vapor-phase process and, in particular, a long catalyst life. A catalyst consisting of antimony pentafluoride supported on activated carbon has now been found to provide the basis for a novel vapor-phase process for the fluorination of isoflurane to desflurane using hydrogen fluoride. The process operates with a long catalyst life, high conversion, and high selectivity.

INTRODUCTION

Desflurane, 2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane (**1**, Scheme 1), is an important inhalation anaesthetic. It is considered to be particularly safe due to its very low level of metabolism within the human body and is especially suited for administration in outpatient procedures due to the rapid rate of patient recovery from anaesthesia.[1]

Various routes to the preparation of desflurane have been disclosed in the literature and these have been reviewed.[1]

There are several known processes for manufacturing desflurane by the reaction of isoflurane or related substrates with hydrogen fluoride catalyzed by Lewis acids.

In an early version of this procedure,[2] the substrate, $CF_3CHFOCH_3$, was initially chlorinated to $CF_3CHFOCHCl_2$. The chlorinated compound was then reacted with anhydrous hydrogen fluoride using antimony pentachloride as a catalyst (Scheme 1).

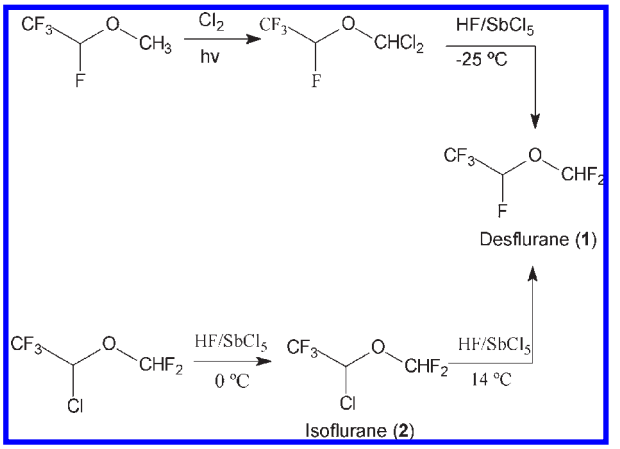
Interestingly, the second step was particularly facile as it was found difficult to stop the reaction at $CF_3CHFOCHClF$, which had been the target compound of this work. However, this is not, at present, a commercial route to desflurane due to the difficulty of accessing the starting ether, $CF_3CHFOCH_3$.

Desflurane can also be prepared by the liquid-phase reaction of isoflurane (**2**, Scheme 1) with excess hydrogen fluoride in the presence of an antimony pentachloride catalyst.[3a,b] Under these conditions, a relatively high yield of desflurane was achieved, and this is the current commercial route to desflurane.

In more recent work,[3c] the use of antimony pentafluoride, instead of antimony pentachloride, has been described and is carried out in a similar manner to the above, allowing the use of a lower excess of hydrogen fluoride. The liquid-phase antimony pentahalide procedures to desflurane from isoflurane are batch procedures, in which there were no reports that the catalyst could be reused.

A proposed mechanism for the fluorination of isoflurane with hydrogen fluoride and a Lewis acid catalyst, along with the reported byproduct, is given in Scheme 2 where Lewis acid (LA) = $SbCl_nF_{5-n}$, $n = 0-2$.

Scheme 1. Preparation of desflurane



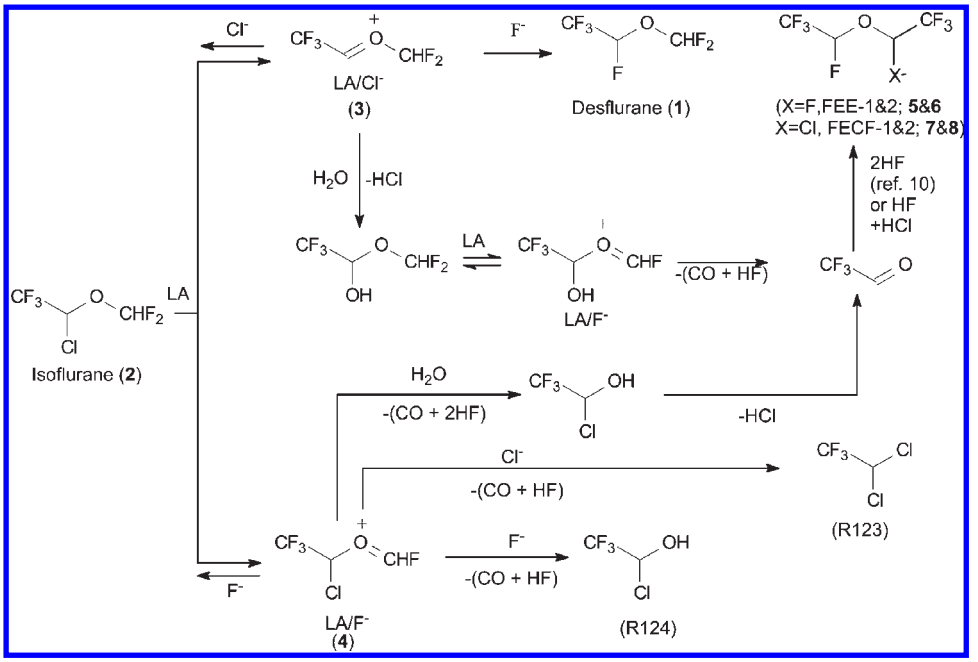
The observed lower activity of the ethyl chlorine is due to its deactivation by the neighboring trifluoromethyl group, i.e. the formation of cation (**4**, Scheme2) is favored. This cation is further stabilized by an alternative resonance structure in which the lone pair on the fluorine donates to the carbocation centre. A very similar cation to **4** derived from desflurane by reaction with antimony pentafluoride has been characterized.[4]

The greater activity of the methyl chlorines to fluorination has been previously exploited in the fluorination of the trichloro substrate, $CF_3CHClOCHCl_2$, as a route to isoflurane (Scheme 1).[5]

Received: November 30, 2010
Published: March 15, 2011

dx.doi.org/10.1021/op100318b | *Org. Process Res. Dev.* 2011, 15, 585–592

Scheme 2. Proposed reactions occurring in the fluorination of isoflurane with hydrogen fluoride to desflurane in a Lewis acid-catalyzed system



A vapor-phase process has been described,[6] in which an isoflurane and hydrogen fluoride mixture in the vapor phase is passed over a chromia catalyst bed at 140 or 170 °C. At the higher temperature a significant amount of cleavage of the carbon—oxygen bond occurs to give about 10% of fragmentation products. Very little fragmentation occurs at the lower temperature, but the conversion is only about 50%. This process, though, does have the benefits of being continuous with a much more efficient catalyst use.

The use of a continuous flow process is very attractive for a commercial production process. It offers many well-known advantages over a batch process, e.g. steady-state conditions (resulting in better process control), smaller reactors and ancillary equipment, less waste, and less down time.

Therefore, an alternative catalyst system for the vapor-phase reaction was sought that would avoid the problems of low conversion or high fragmentation.

The use of antimony pentahalides, particularly antimony pentafluoride, intercalated into graphite or activated carbon as mild, but effective, fluorination catalysts has been reported.[7a,b,9] In these intercalates, the antimony pentahalides act as electron acceptors, so the intercalation complexes are weaker catalysts than the free halides, but more stable to reduction.[7a,8] There could thus be an improved catalyst life, but with a lower activity, relative to the free antimony pentahalides. Hence, they are potential catalysts for the high-temperature vapor-phase fluorination of isoflurane to desflurane. It was, therefore, decided to investigate these further for possible application to a continuous flow process.

RESULTS AND DISCUSSION

In the investigation of the catalyst, the particular points of interest were the yield, conversion, productivity, catalyst life, reaction conditions, and the effect of water.

In order to carry out this work, a rig had to be constructed suitable for studying vapor-phase reactions and also being safe to operate, given the known highly corrosive nature and toxicity of hydrogen fluoride. A schematic of the rig used is shown in Figure 1.

Isoflurane is a volatile, colorless liquid with a relatively low boiling point (49 °C[1]). The syringe pump used for feeding isoflurane was found to operate satisfactorily and gave an accurate flow.

The AHF was fed as a vapor from a cylinder mounted on a balance and was more difficult to control, as the flow rate had to be calculated from the balance reading and could not be read instantaneously. In addition, care had to be taken not to disturb the cylinder on the balance, as this would affect the tare.

The catalyst was charged through a side port at the top of the tubular reactor. The catalyst was prepared using the procedure outlined in Scheme 3. Teflon was found to be suitable material of construction for handling antimony pentafluoride, whereas polypropylene was not.

A tube, carrying four thermocouples, ran through the centre of the reactor, so that temperatures at different depths of the bed could be measured. Under running conditions, the temperature at the top of the bed was found to be 10—20 K below the temperatures in the middle and at the bottom of the bed. The temperature given in the results is taken in the middle of the bed (thermocouple 4).

The recovered organics were treated with aqueous alkali to ensure that they were neutralized and then were analyzed by gas chromatography. No further purification was carried out on the crude product before it was analyzed.

A preliminary run was carried out to investigate the activity of the catalyst and to give an indication of the suitable conditions. The results obtained are summarized in Table 1.

dx.doi.org/10.1021/op100318b |*Org. Process Res. Dev.* 2011, 15, 585–592

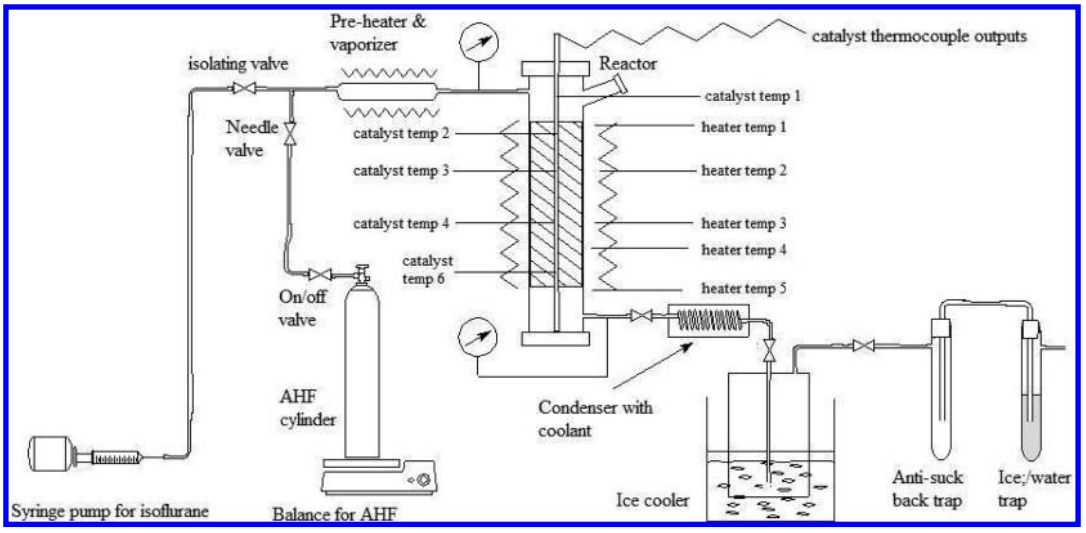
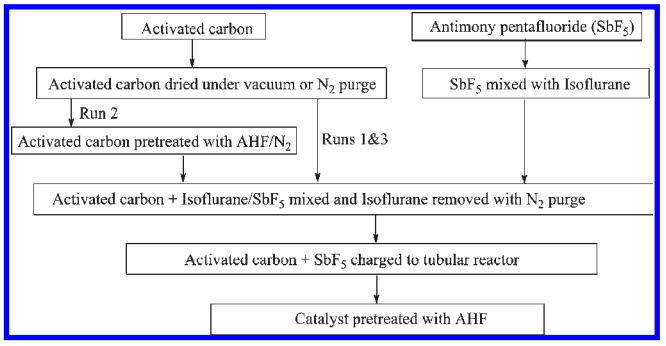


Figure 1. Schematic of the rig used for the study of the vapor-phase fluorination of isoflurane to desflurane.

Scheme 3. Flow diagram for the procedure used for preparing the SbF5/carbon catalyst



There is a continuous increase in conversion as the temperature is raised, until about 150 °C, above which there is some drop in conversion. It was therefore decided to work in the temperature range 135−150 °C.

Three experiments were carried out, and the conditions used are summarized in Table 2.

The overall results for each run are summarized in Table 3 and the performance against time is shown in Figure 2.

The results show that a high conversion giving mainly desflurane is readily achieved with this catalyst.

After the first few hours the performance of the catalyst is very steady, and in run 2, high conversion is sustained across the full 150 h of the run. There is thus no evidence of any loss of catalyst activity, indicating that it is not being degraded or fouled by solid deposits over this time.

Localized heating on the catalyst should not be a problem, as the fluorination reaction of isoflurane to desflurane has been reported to be mildly endothermic.[3a,b] This will help the catalyst lifetime as it would reduce the likelihood of thermal degradation on the catalyst.

Initially, there is a very high conversion of the input isoflurane, which declines over the first 5 h and then stabilizes. The observed change in catalyst activity indicates a reduction in Lewis acidity in this period. A possible reason is the initial presence of some free antimony pentafluoride, which then becomes intercalated into the carbon. Some chlorination of the intercalated antimony pentafluoride cannot be excluded, but chlorination must be limited; otherwise continuing catalyst degradation due to reduction would be observed.

The HF:isoflurane ratio was lower in run 3 than in the other two runs; however, there was no significant difference in performance. In run 2, the drop in the HF feed ratio at 110 h caused some drop in conversion, which was reversed on restoring it to its previous value. For the last 10 h, the temperature of the reactor was raised by 5−10 K, which caused a rise in conversion.

Table 1. Summary of results for preliminary experiment

time (h)	temp. °C	residence time (s)[a]	iso:AHF molar ratio iso = 1	des % area in crude product	iso % area in crude product
2.0	60.0	25.8	1.1	2.2	95.3
4.8	60.0	31.0	1.8	0.0	100.0
4.8	60.0	36.5	1.9	0.6	99.0
7.3	98.0	40.5	2.1	7.1	92.6
10.0	98.0	41.2	1.7	8.2	91.5
13.3	110.0	55.0	1.7	16.3	83.7
17.3	110.0	29.9	2.5	13.6	84.4
19.3	120.0	31.6	1.0	26.5	73.2
21.3	135.0	21.3	3.3	53.7	43.4
23.8	136.0	23.5	2.9	44.5	53.2
26.8	150.0	20.1	3.9	67.2	30.5
29.8	170.0	14.2	3.8	66.2	31.9
32.8	170.0	26.9	2.2	54.4	43.7
34.8	170.0	25.6	2.2	54.9	43.1
37.5	176.0	18.1	3.5	49.9	48.5
40.0	170.0	20.6	3.4	48.0	50.8
42.8	170.0	28.5	4.8	65.7	33.1

catalyst charge:	25.0 g containing 0.83 mmol/g of SbF_5
catalyst density:	0.67 g/cm^3
average HF feed rate	2.62 g/h

[a] The residence time calculation assumes ideal gas properties and makes no allowance for the volume of the catalyst. The residence time is given in seconds (s).

dx.doi.org/10.1021/op100318b |*Org. Process Res. Dev.* 2011, 15, 585–592

Table 2. Reaction conditions of the three runs carried out

reaction conditions	run 1	run 2[a]	run 3
HF:isoflurane molar feed ratio	1:2.81	1:2.81	1:2.53
HF feed rate g/h (mol/h)	5.0 (0.25)	5.0 (0.25)	4.4 (0.22)
iso feed rate g/h (mol/h)	16.4 (0.089)	16.0 (0.087)	16.0 (0.087)
reactor temperature (mid-bed), °C	135	135	135
antimony pentafluoride charge, g (mol)	31.0 (0.143)	28.0 (0.129)[b]	23.0 (0.106)
activated carbon charge, g	60	75[b]	60
SbF_5/carbon loading, mmol/g	1.6	1.3	1.3
residence time, s	~56	~58	~64
total run time, h	40	150	35

[a] Run 2 was run in a steady state for 110 h and was then continued for a further 40 h in order to test variations in the hydrogen fluoride feed rate and the reactor temperature. [b] Some catalyst (15 g) was not charged to the reactor.

Table 3. Preparation of desflurane from the isoflurane reaction with HF, over SbF_5/carbon catalyst in the vapor phase; summary of results[a]

run	% des in crude product	% iso in crude product	reaction yield	convn. (%)	sel. (%)	organic molar balance (%)	comments
1 (40 h)	81.6	11.8	59.8	92.1	65.0	71.4	no equilibration time, but 6 h within run omitted
2 (150 h)	81.3	17.9	72.6	85.5	85.0	87.4	after 10 h equilibration
3 (35 h)	81.1	15.6	65.1	88.6	73.5	76.5	after 6 h equilibration

[a] The following definitions are used: Reaction yield = (mol desflurane out)/(mol isoflurane in). Conversion (convn.) = (mol isoflurane consumed)/(mol isoflurane in). Selectivity (sel.) = (mol desflurane out)/(mol isoflurane consumed). Organic molar balance = (mol all products out − as isoflurane equivalents)/(mol isoflurane in).

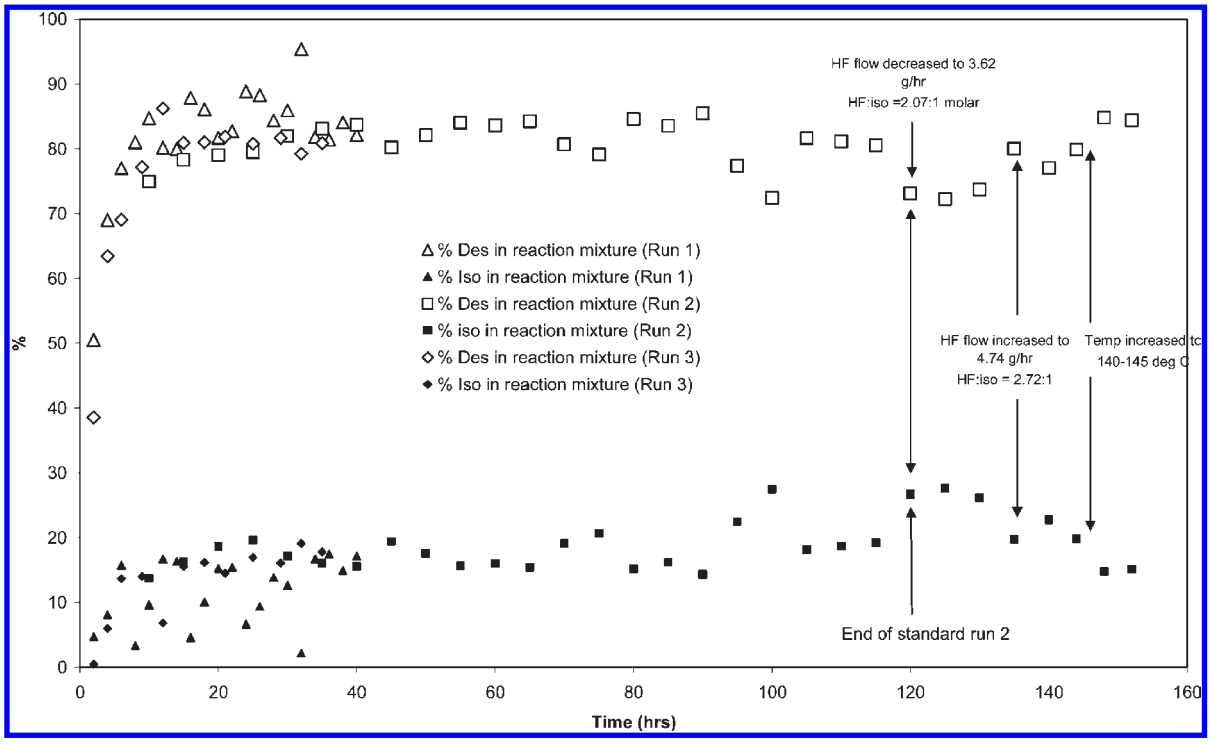


Figure 2. Fluorination of isoflurane with HF over an antimony pentafluoride supported catalyst. Plot of desflurane and isoflurane in crude reaction product against time.

The effects observed though were small and are not conclusive. The effect of pressure was not investigated in this study.

In run 2, a selectivity of 85% was observed. As very little byproduct was observed, it is suspected that the possible selectivity with a higher mass balance could be >90%.

Lower selectivities are observed for run 3 and particularly for run 1. However, these results are in line with the lower organic balances achieved in these runs and are considered to be due to physical losses. In general, the organic molar balance would be affected by physical loss, decomposition to

dx.doi.org/10.1021/op100318b |*Org. Process Res. Dev.* 2011, 15, 585–592

Table 4. Composition of combined crude product[a] from run 2

component			
formula	acronym/name	GC analysis % area	comments
CF_3CHClF	R124	0.4	main fragmentation product from cleavage of ether linkage
$CF_3CHFOCHFCF_3$ -(1)	FEE-1 (**5**)	0.2	produced by presence of water, significant at beginning of run
$CF_3CHFOCHF_2$	desflurane (**1**)	81.3	
CF_3CHCl_2	R123	nd	not seen in GC
$CF_3CHFOCHClCF_3$ -(1)	FECF-1 (**7**)	0.09	as FEE-1, with chlorine substituent
$CF_3CHFOCHFCF_3$ -(2)	FEE-2 (**6**)	0.09	diastereoisomer of FEE-1
$CF_3CHClOCHF_2$	isoflurane (**2**)	17.9	
$CF_3CHFOCHClCF_3$ -(2)	FECF-2 (**8**)	nd	not seen in GC of combined crude product, but observed as trace in GC−MS; it is a diastereoisomer of FECF-1

[a] Identification by GC−MS.

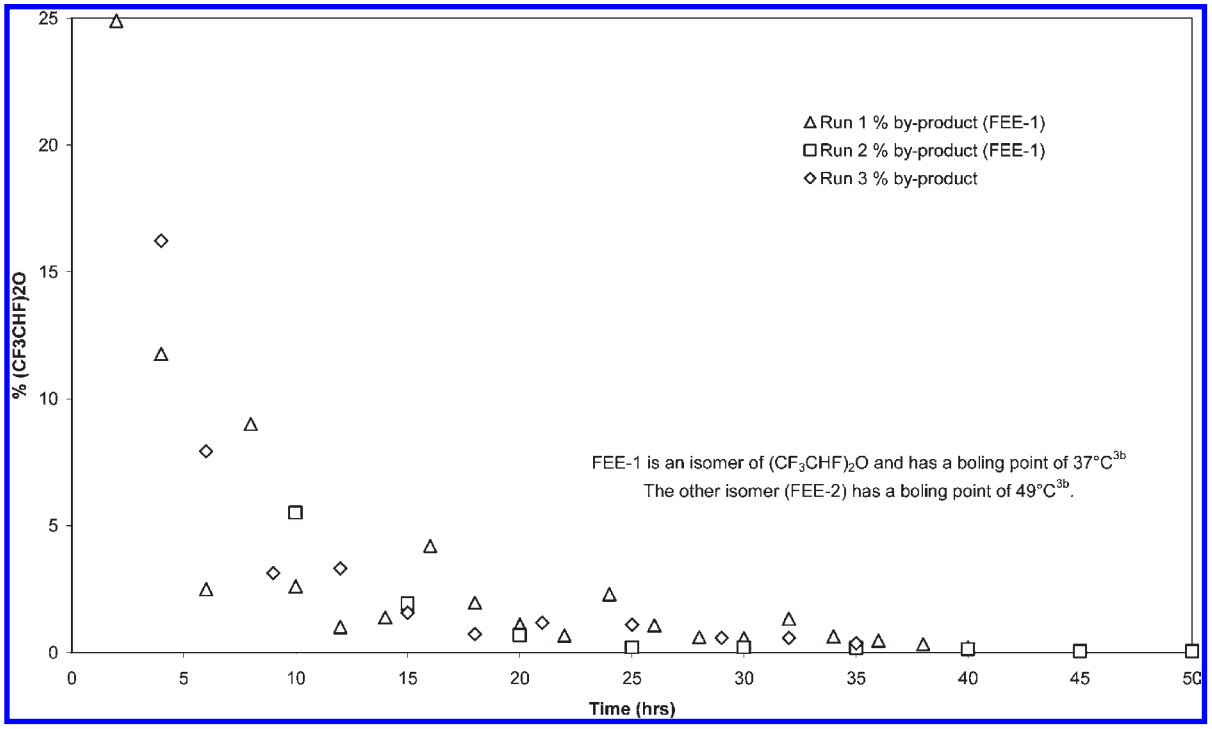


Figure 3. Plot of the formation of the main byproduct FEE-1, $(CF_3CHF)_2O$, against time in the fluorination of isoflurane to desflurane.

nonvolatiles in the reactor, and the production of low volatility byproduct.

A patent[9] claims that prefluorinating the active carbon support with hydrogen fluoride stabilizes metal halide intercalates to high temperatures (up to 185 °C). The possible benefit of prefluorination in this reaction was, therefore, investigated.

In our runs 1 and 3, the catalyst was not prefluorinated, but in run 2 it was. There is no evidence from the runs 1 and 3 that the catalyst was declining in activity over the time that they were run. It therefore appears from these results that the prefluorination is not necessary when antimony pentafluoride is used as the Lewis acid.

No attempt was made in this work to purify the crude desflurane produced. However, it has been reported that this can be done by fractional distillation, and the main impurities are readily separated from desflurane by distillation.[3b] However, it was noted that FEE-2, $CF_3CHFOCHFCF_3$, cannot be separated easily from the recovered isoflurane, and its gradual accumulation results in isoflurane loss.[3b] The low level of this impurity produced is thus an advantage for this process.

The reaction was very clean with only a small amount of byproduct produced. The analysis of the combined crude products for run 2, after washing, is given in Table 4.

The mechanisms of formation of these compounds are shown in Scheme 2.

The main byproduct observed in the crude product is one of the isomers of bis(1,2,2,2-tetrafluoroethyl)ether, FEE-1 (**5**, Scheme 2). The formation of this byproduct would be expected to consume a mole of water for every mole of FEE-1 created. This is a known trace impurity in commercial desflurane

The evolution of the amount of this impurity over the course of the three runs is shown in Figure 3.

Although the presence of water on the catalyst causes the formation of a byproduct, it is also consumed in this reaction and appears to have no effect on the lifetime of the catalyst. The likely

dx.doi.org/10.1021/op100318b |*Org. Process Res. Dev.* 2011, 15, 585–592

mechanism of formation of the byproduct is through the same cationic intermediates that lead to desflurane (Scheme 2), hence the presence of water is causing no noticeable loss in the Lewis acidity of the catalyst.

In run 1 a quantitative result was obtained and indicated that about 1 g of extra water is present at the start of the run and is mainly consumed over the first 20 h. This would indicate that despite the drying regime carried out on the activated carbon, it still contained about 1.7% w/w water at the commencement of the run.

The other main bis-ethers (FECF-1 and FEE-2) are also observed to be higher at the start of the runs. In run 2, at time =10 h, FECF-1 was at 1.4% and FEE-2 was at 2.8%, but they rapidly dropped to very low levels. This is expected as these are produced from the same or closely related reactions.

In addition, the main fragmentation product, R124, reached a maximum at 15 h of 1.3% and then dropped rapidly to 0.2−0.4%. This suggests that water can also promote fragmentation.

CONCLUSIONS

A continuous vapor-phase process has been found for the fluorination of isoflurane to desflurane with hydrogen fluoride. The process offers advantages of being a continuous process over the existing batch processes. It should be readily suitable for large-scale manufacture and would lead to better process control and reproducibility, which is particularly important for a pharmaceutical product.

The catalyst used is readily prepared from activated carbon and antimony pentafluoride. The long catalyst life results in much less antimony-containing waste to be disposed of than the existing processes and hence brings environmental benefits.

The process operates with a high conversion and selectivity. After an initial equilibration period, very few byproducts are formed, simplifying the subsequent purification and reducing waste. In particular, very little fragmentation is observed.

Finally, an experimental system has been developed that can be used in the study of other continuous vapor-phase reactions, particularly those requiring hazardous hydrogen fluoride.

EXPERIMENTAL SECTION

Isoflurane was from commercial material made by Piramal Healthcare Limited (PHL). It was dried over type 4A molecular sieves prior to use. The antimony pentafluoride was supplied by Sigma-Aldrich and used without further purification. The activated carbon used was an extrudate of diameter 1.5−2 mm, length 3−4 mm, and density 0.4−0.45 g/cm^3.

The analysis was carried out on a gas chromatograph (HP 6890, series 2, FID), using the column and conditions specified in the USP monograph (USP29): The gas chromatograph was equipped with an FID detector and a 2.4 mm × 6.1 m stainless steel column packed with 25% phase G16 (polyethylene glycol 20 M) on 80−100-mesh support S1A (flux calcined siliceous earth flux). Helium was used as the carrier gas at a flow rate of 20 cm^3/min. The column temperature was maintained at 75 °C, the injection port at 200 °C, and the detector at 250 °C.

The gas chromatographic analyses were uncalibrated and are reported as area %. A standard sample was run, and it was found that the relative response factor for isoflurane was 11% greater than that for desflurane. Hence, the area % results would be about 0.5% too low for desflurane at high and low concentrations, and the 0.5% too high for isoflurane. At about 50% concentration the difference would rise to 2.4%. The precision of the analysis is typically ±0.3% or greater. These response factors have not been incorporated into the results as the linearity was not established.

Compounds were identified using GC−MS on a Shimadzu GC−MS QP2010, using an AB-Inowax (60 m × 0.32 mm id × 0.50 μ film thickness) column made by Abelbonded.

Before injecting samples into the GC or GC−MS analyzers, the syringe needles and the samples were chilled to allow for the low boiling point of desflurane (23.5 °C[1]).

Equipment: A schematic of the rig used is given in Figure 1.

The isoflurane was fed as a liquid at a controlled rate by a syringe pump (Teledyne Isco, model 500 D) and mixed with HF vapor. The mixture then passed to a vaporizer at 70−80 °C. The AHF was fed as a vapor from a cylinder (∼5 kg) mounted on a balance. The AHF flow was controlled by a needle valve

The reactor consisted of an Inconel tube of 2.5 cm diameter with a catalyst bed length of 35.6 cm and total length of about 61 cm. The total volume of catalyst in the reactor was thus 170 cm^3, after allowing for the thermocouple volume.

In the reactor, there were four thermocouples distributed along the length of the catalyst bed (thermocouples 1 and 5 were not used and are not shown). The thermocouples measured the temperature near the centre of the bed. The thermocouples were contained within a 0.625 mm (1/4 in.) Inconel tube passing down the centre of the bed. Type K (chromel−alumel) thermocouples were used. Thermocouple 2 measured the temperature at the top of the bed, and thermocouple 6, the temperature at the bottom, while thermocouples 3 and 4 measured the interior temperatures of the bed. Thermocouple 4 was used for recording the typical temperature of the bed.

The reactor had a wide 'Y' junction with a side arm at the top, where the catalyst was loaded.

The vapor exiting the reactor was then passed through a water-cooled condenser. The reaction mixture was then collected in a plastic (polypropylene) container, cooled in crushed ice. The residual noncondensable products were then passed through an antisuck back-trap before being bubbled through an ice−water mixture or aqueous alkali and then vented. The cooler, collection vessel, and trap were connected using Teflon tubing.

The organic product from the cooled plastic container was then separated by phase separation from the aqueous layer and combined with any organic condensate from the final scrubber. Once neutral, no further purification of the organic material was carried out before it was analyzed by GC.

The procedure used to prepare the catalyst is summarized in Scheme 3. The activated carbon was dried under vacuum for the preliminary temperature investigation, runs 1 and 3, as detailed below. In run 2 it was dried in the reactor under a nitrogen flow and then pretreated with gaseous anhydrous hydrogen fluoride and nitrogen. The prepared activated carbon was then mixed under nitrogen with the isoflurane/antimony pentafluoride mixture, and the isoflurane was removed with a nitrogen purge. The catalyst was then charged to the reactor and treated with nitrogen and gaseous hydrogen fluoride. The system was then pressure tested with nitrogen (2.4−3 barg) to ensure that it was leak free.

Investigation of the Effect of Temperature on the Reaction Rate. A 100 cm^3 polypropylene conical flask at room temperature was gently purged with nitrogen. Into the flask was added isoflurane (25.0 g, 0.136 mol) and antimony pentafluoride (5.0 g, 0.0231 mol). White fumes were observed along with some discoloration of the solution. (Polypropylene was not

considered stable enough for handling antimony pentafluoride and in the further experiments, Teflon was used.) Activated carbon (15 g) was then immediately added to the flask and the mixture shaken. The activated carbon had been previously dried under a vacuum for 2 h at 70−75 °C. The isoflurane was then driven off with a nitrogen purge. The final weight of the catalyst was 27.9 g, indicating that some isoflurane remained. The catalyst concentration was thus 0.83 mmol/g.

The catalyst (25.0 g) was charged to the reactor and the system pressure tested. The catalyst was conditioned by purging with nitrogen (50 cm^3/min) for 1 h at ∼50 °C. It was then purged with hydrogen fluoride (2.2 g/h) for 2 h at 60−65 °C.

The isoflurane was fed at varying rates from 4.5 to 13.5 g/h and the HF at rates of 1.1−4.5 g/h. The temperature of the reactor was raised in fixed steps from 60 to 170 °C. The recovered condensate was routinely analyzed by GC.

Run 1: Vapor-Phase Fluorination of Isoflurane Using Supported Antimony Pentafluoride: (40 h). Into a Teflon container (500 cm^3), fitted with a lid and two inlets, was charged dried isoflurane (130 g). The system was then flushed with nitrogen. Antimony pentafluoride (31.0 g, 0.143 mol) was then charged under nitrogen.

Activated carbon (60.0 g) (that had been previously dried under high vacuum at 80 °C for 4 h) was then charged under a nitrogen stream. The catalyst loading was thus 1.1 mmol/g. During the addition of the activated carbon an exotherm was observed.

The catalyst was then charged to the reactor under a nitrogen flow.

After charging, the reactor was pressure tested. The reactor was then purged with nitrogen for about 1.5 h to remove isoflurane. The HF flow was then commenced, 5.0 g/h (0.25 mol/h) and the nitrogen flow stopped. The reactor was heated to 135 °C over 2 h. The isoflurane feed, 16.4 g/h (0.089 mol/h) was then commenced.

The crude organics were collected over 2-h periods and analyzed. The feed was run for a total of 40 h.

The feeds were isoflurane, 556.3 g (3.015 mol) and anhydrous hydrogen fluoride, 170.8 g, (8.54 mol). (In this run, 6 h of running has been omitted from the input and output totals as not all output weight was recorded).

The weight of crude products recovered was 371.5 g with average contents of desflurane 81.6%, isoflurane 11.8%, and FEE-1 3.2%. The reaction yield to desflurane was thus 59.8% with a conversion of 92.1% and an overall selectivity to desflurane of 65.0%.

Run 2: Vapor-Phase Fluorination of Isoflurane Using Supported Antimony Pentafluoride (150 h). Activated carbon was placed in a tubular reactor and dried at 180 °C for 6−7 h under nitrogen flow ∼100 cm^3/min. Then hydrogen fluoride gas was passed over it at 120 °C at a rate of 12 g/h, along with nitrogen, at 50 cm^3/min for 8 h. The hydrogen fluoride feed was then stopped and the nitrogen flow continued for a further 8−10 h.

The activated carbon was then unloaded from the reactor under nitrogen flow in a self-sealing plastic bag, while keeping nitrogen flow inside the bag. The bag was then closed.

A Teflon flask (500 cm^3 capacity) was nitrogen purged, and previously cooled isoflurane (100.0 g, 0.542 mol) was added. Antimony pentafluoride (28.0 g, 0.129 mol) was then charged to the isoflurane.

The treated activated carbon (75.0 g) was then charged to the antimony pentafluoride solution under nitrogen, and the mixture was allowed to stand for 5−10 min, without agitation. Some white fumes were observed at this stage. The assembly was then agitated gently for several minutes. The loading was 1.3 mmol/g. The assembly was then flushed with nitrogen to drive off as much isoflurane as possible. Some catalyst (15.0 g) was set aside, and the rest was charged under nitrogen to the tubular reactor.

After charging, the reactor was pressure tested and purged with nitrogen for about 1 h to remove solvent. An HF flow was then commenced (3−4 g/h), the nitrogen flow was discontinued after cofeeding with HF for 1 h. The reactor was then heated to 50−70 °C for 3−4 h The temperature was then raised to 100−120 °C, and the HF feed was continued for a further 1−3 h. The temperature was then raised to 135 °C before commencing the isoflurane feed. The pressure of the system was 0−0.2 barg.

The HF was fed at a rate of 5.0 g/h (0.25 mol/h), and the isoflurane, at 16.0 g/h (0.087 mol/h), with a resulting molar feed ratio of isoflurane/HF of 1:2.88. The temperature was maintained at 135 °C in the reactor.

The product was condensed and neutralized as described above and routinely sampled and analyzed. The run was continued for 110 h. After 10 h that was required for stabilization, the analysis results across the run were consistently 80−83% desflurane with most of the balance being isoflurane. The average molar feed ratio of isoflurane/HF over this period was thus 2.82:1.

The total feeds after the period of stabilization was isoflurane, 1595 g (8.645 mol), and anhydrous hydrogen fluoride, 488 g (24.40 mol).

The weight of crude products recovered was 1296 g with an average desflurane content of 81.3% and an average isoflurane content of 17.9%. The reaction yield to desflurane was thus 72.6% with a conversion of 85.5% and an overall selectivity to desflurane of 85.0%.

The run was then continued for a further 40 h in order to test variations in some of the parameters.

Between 115 and 130 h the HF feed was reduced to 3.62 g/h, while the isoflurane feed was maintained at its previous rate. The HF:isoflurane molar feed ratio was thus reduced to 2.07:1. After 130 h the HF feed was restored to approximately its previous rate (4.74 g/h).

For the last 10 h (140−150 h) the temperature was raised to 140−145 °C.

The run was then terminated.

Run 3: Vapor-Phase Fluorination of Isoflurane Using Supported Antimony Pentafluoride (12 h). Into a Teflon container (500 cm^3), fitted with a lid and two inlets was charged dried isoflurane (100 g). The system was then flushed with nitrogen. Antimony pentafluoride (23.0 g, 0.106 mol) was then charged under nitrogen.

Activated carbon (60.0 g) (that had been had been dried as in run 1) was then charged under a nitrogen stream. The catalyst loading was thus 0.8 mmol/g.

The catalyst was then charged to the reactor and pressure tested. The catalyst was then fluorinated with HF as described in Run 1.

The HF was fed at a rate of 4.4 g/h (0.22 mol/h), and the isoflurane, at 16.0 g/h (0.087 mol/h), with a resulting molar feed ratio of isoflurane/HF of 1:2.54. The temperature was maintained at 135 °C in the reactor.

The product was condensed and neutralized as described in Run 1 and routinely sampled and analyzed. The run was

continued for 35 h. After allowing 6 h required stabilization the average analysis results across the run for the reactor product was 81.1% desflurane with 15.6% isoflurane. The FEE-1 content across the run was 1.2%.

The total feeds after the period of stabilization was isoflurane, 505.3 g (3.238 mol) and anhydrous hydrogen fluoride, 139.1 g (6.954 mol), giving an average molar feed ratio of HF/isoflurane of 2.15:1.

The weight of crude products recovered in this time was 369.5 g. The reaction yield to desflurane was thus 65.1% with a conversion of 88.6% and an overall selectivity to desflurane of 73.5%. The organic balance was 76.5%.

AUTHOR INFORMATION

Corresponding Author

owenscotgerm@gmail.com

Present Addresses

[§]5 Hawke Road, Kewstoke, Weston super Mare, BS22 9LB, United Kingdom.

ACKNOWLEDGMENT

We thank Dr. B. Narsaiah (Scientist - Fluoro organic division - IICT, Hyderabad) for useful discussions and facility support; and Mr. P. V. S. S Srinivas - IICT Technical Officer, for assistance in conducting the laboratory experiments.

REFERENCES

(1) Halpern, D. F. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolski, L. M., Eds.; Elsevier: Amsterdam, 1993; p101.

(2) Siegmund, G. 1,2,2,2-Tetrafluoroethyl chlorofluoromethyl ether. German Patent DE 2361058, 1973.

(3) (a) Cicco, C. F. Process for the production of 1,2,2,2-tetrafluoroethyl difluoromethyl ether. U.S. Patent 5,026,924, 1989. (b) Rozov, L. A.; Lessor, R. A. Preparation of desflurane. U.S. Patent 6,800,786, 2002. (c) Terrell, R. C.; Levinson, J. Process for the production of 1,2,2,2-tetrafluoroethyl difluoromethyl ether. WO/2006/055749, 2004.

(4) Petrov, V. A.; Davidson, F. *J. Fluorine Chem.* **1999**, *95*, 5.

(5) Terrell, R. C. 1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether. U.S. Patent 3,535,388, 1967.

(6) Swinson, J.; Jones, B.; Graham, D.; Pavri, N. Synthesis of fluorinated ethers. WO/2006/076324, 2005.

(7) (a) Lalancette, J. M.; Lafontaine, J. *J. Chem. Soc., Chem. Commun.* **1973**, 815. (b) Lalancette, J. M. Graphite intercalated antimony pentafluoride. U.S. Patent 3,950,262, 1973.

(8) Dresselhaus, M. S. *Mater. Sci. Eng.* **1988**, *B1*, 259.

(9) Elsheikh, M. Y.; Chen, B. Fluorination catalysts. U.S. Patent 6,074,985 1999.

(10) Burgess, L.; Butcher, J. L.; Ryan, T. A.; Clayton, P. P. Production of hydrofluorocarbons. U.S. Patent 5,696,308 1991, (particularly experiment example 7).

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on March 15, 2011. A change was made to Figure 1 and the corrected version was reposted on March 24, 2011.