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Microwave fluorination: a novel, rapid approach to fluorination with Selectfluor®

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Abstract

Fluorination of electron rich aromatic systems with electrophilic fluorination reagents such as Selectfluor® and Accufluor® is a well-established process. Herein we report results from investigations into the use of such procedures to perform rapid, small-scale fluorinations under microwave irradiation. We have investigated the transformation with a range of different substrates and discuss the effects of two key factors, namely reaction time and choice of fluorination reagent. The use of Selectfluor® in acetonitrile at 150 °C with microwave heating for 10 min affords products in comparable yields to those obtained by prolonged heating in acetonitrile at its reflux temperature.

Keywords: Electrophilic fluorination; Fluorination reagents; Selectfluor; Accufluor; Microwave heating

1. Introduction

Fluorination of electron rich aromatic systems with electrophilic fluorination reagents such as Selectfluor® (**1**) [1] and Accufluor® (**2**) [2] is an established process which has been well studied and is the subject of several useful and informative reviews [3–5] (Fig. 1).

Such processes are of interest to us as many agrochemicals contain fluorine, due to the unique biological properties which fluorine imparts [6]. Therefore, new general methods to incorporate fluorine atoms into organic molecules are an important goal in our research.

Many fluorinations with Selectfluor® (**1**) occur at room temperature or below, such as the preparation of fluoromalonates [7] and reaction with silyl enol ethers to give α-fluorocarbonyl products [1]. However many procedures (such the electrophilic fluorination of aromatic rings) require harsher conditions, typically refluxing in MeCN for extended periods, to effect these transformations in reasonable yields [1]. With the advent of microwave reactors, many synthetic processes which were previously low yielding or required extended reaction times at elevated temperatures have been transformed into protocols typically requiring only minutes to achieve comparable, or in some cases superior, results [8]. While the literature does contain reports of microwave fluorination procedures, those published previously have been nucleophilic fluorinations, such as epoxide ring opening with fluoride [9] and halogen exchange reactions [10–12]. We aimed to develop a novel protocol using reagents such as Selectfluor® (**1**) in a microwave reactor, which would enable greater access to a range of fluorinated aromatics and hence be of synthetic utility in agrochemical and pharmaceutical discovery.

2. Results and discussion

Despite initial concerns over the thermal stability of Selectfluor® (**1**) [13], especially in bulk [14], the report of Banks et al. [7] that such compounds were thermally stable to temperatures above 150 °C, gave us some cause for optimism. Our early experiments focused on the fluorination of anisole since electrophilic fluorination with (**1**) had previously been reported by Lal [1] using the standard conditions of refluxing in MeCN.

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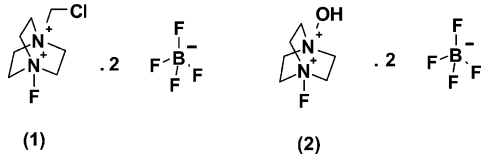


(1) (2)

Fig. 1. Structures of Selectfluor® and Accufluor®.

Table 1
The effect of reaction time on product yield for fluorination of anisole

Recovered material[a]	Time (min)		
	10	30	60
Anisole (3) (%)	26	21	8
(**4**) (%)	18	14	16
(**5**) (%)	12	18	10
(**6**) (%)	2	3	3
Recovery (%)	58	56	37
Combined yield (%)[b]	32 (43)	35 (56)	29 (32)

[a] Data obtained using GC method in experimental in combination with ^{19}F NMR data published by Laali et al. [15] to identify the isomers formed.
[b] Yield based upon recovered starting material shown in parenthesis.

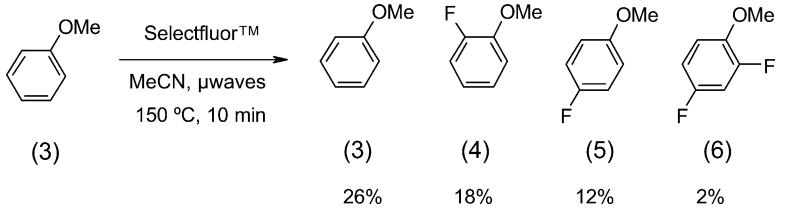
Thus, anisole (0.5 mmol) in MeCN (2.5 mL) was added to a microwave tube containing Selectfluor® (0.5 mmol) and heated to 150 °C for 10 min. Much to our relief, no unusual temperature or pressure fluctuations indicative of thermal breakdown of the fluorinating reagent were observed and the reaction appeared to proceed smoothly. The results were analysed by GC using the procedure outlined in Section 4.

Pleasingly, good levels of fluorination had occurred with the product mixture containing anisole (**3**) (26%), 2-fluoroanisole (**4**) (18%), 4-fluoroanisole (**5**) (12%) and 2,3-difluoroanisole (**6**) (2%), giving a recovery of 58% and a combined product yield of 32% (43% if based on recovered starting material). This was a very promising initial result (Scheme 1). It was decided to investigate the effect of increased reaction time upon this process, with a view to improving the conversion of starting material. Thus, two more reactions were performed varying only the reaction time (30 and 60 min, respectively). The results are presented in Table 1.

The most striking result from these data is that although increasing reaction time correlates well with consumption of anisole, the actual yields vary remarkably little with increased reaction time, although it does seem to have some effect on product distribution. Clearly the processes occurring here are somewhat complex but it was concluded that greater quantities of fluoroanisole were being formed with increased reaction time, but that those products are themselves then being consumed to form polymeric and volatile polyfluoro species which cannot be easily quantified or identified.

We were interested to see if a similar trend was discernable with other electron rich aromatic species and so we repeated these experiments with toluene, phenol and dibenzofuran as substrates. The results of these experiments are summarized in Table 2.

From these data it is clear that fluorination under these conditions is a general process for electron rich aromatics and not restricted to anisole. In all the substrates examined, fluorination results were comparable with those obtained using the Selectfluor® under reflux conditions, in a fraction of the time [1,15]. Especially gratifying are the observations

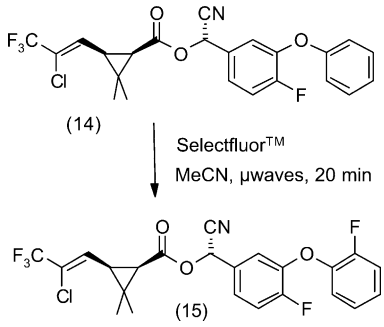


Scheme 1.

Table 2
The effect of reaction time on product yield for fluorination of toluene, phenol and dibenzofuran

Time (min)	Toluene[a]						Phenol[a]					Dibenzofuran[b]					
	Starting material (%)	2-F (%)	4-F (%)	2,4-F (%)	Recovery (%)	Yield[c] (%)	Starting material (%)	2-F (%)	4-F (%)	Recovery (%)	Yield[c] (%)	Starting material (%)	4-F (%)	5-F (%)	6-F (%)	Recovery (%)	Yield[c] (%)
10	51	34	14	1	100	49 (100)	18	10	6	34	16 (43)	25	3	1	4	33	8 (11)
30	45	37	15	1	98	53 (96)	17	11	8	36	19 (36)	19	3	1	3	26	7 (9)
60	23	20	7	1	51	28 (36)	18	16	8	42	24	16	3	1	3	23	7 (6)

[a] Data obtained using GC method in experimental and suitable commercially available fluoro-compounds as standards for reference.
[b] Data obtained using GC method in experimental in combination with ^{19}F NMR data published by Laali et al. [15] to identify the isomers formed.
[c] Yield based upon recovered starting material shown in parenthesis.



Scheme 2.

made from the fluorination of toluene, a process with good yields (53–28%) and excellent recoveries (100–51%), which augurs well for the use of this technique with a wider range of less electron rich substrates (Scheme 2).

It seems evident with toluene, phenol and dibenzofuran as with anisole, that while increasing reaction time increases consumption of starting material it offers little real advantage to the reaction in terms of yield. It is worthwhile noting that in the cases of toluene, anisole and phenol we were not able to detect formation of the *meta*-fluoro-isomer, with only the expected *ortho*- and *para*-isomers plus small amounts of the 2,4-difluoro compounds being observed.

Another parameter we were keen to investigate was the choice of fluorination reagent. Many different electrophilic fluorine sources have been documented in the literature in recent years and given the wide structural differences between them we wondered if any one 'F^+ source' would be optimal. A range of commercially available fluorination sources was therefore investigated under identical conditions (a 10 min reaction in MeCN at 150 °C). The results of this investigation are summarized in Table 3.

It was found that Selectfluor® and Accufluor®, the two structurally related fluorination reagents commercialised by Air Products Inc., both gave similar results in these experiments with good conversion and satisfactory amounts of products formed (32 and 42% combined yield, respectively), with only small amounts of unreacted starting material being detected (26 and 7%). With the exception of 1,1-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (**7**) [16], the results from all the other fluorination systems examined were disappointing with less than 5% product formation in all cases. (**7**) was clearly reactive under microwave conditions giving a 21% yield and 70% conversion of starting materials: this compares to the reported 65% yield and 85% conversion under standard conditions [16]. This suggests that under microwave heating at 150 °C, over-reaction and tar formation was occurring.

It is perhaps not surprising that reactions with *N*-fluoropyridinium triflate (**8**) and *N*-fluoro-2,4,6-trimethylpyridinium triflate (**9**) were poor yielding as Umemoto et al. [17] reported that such reagents were inferior to methoxy-carbonyl substituted examples, or their bipyridinium counterparts like (**7**) [16]. However, their reactivity under microwave conditions was unknown.

N-Fluorobenzenesulfonimide (**10**), in contrast, has been reported by Differding and Ofner [18] to facilitate electrophilic fluorination of anisole; however to achieve good yields 22 equivalents of anisole are required, with heating to 150 °C for 5 h in the absence of solvent. The same senior author also introduced 2,3-dihydro-3,3-dimethyl-2-fluoro-1,2-benzisothiazole-1,2-dioxide (**11**) but its use was limited to reaction with carbanions [19]. *N*-Fluoropyridinium pyridine heptafluorodiborate (**12**) [20] and *N*-fluoro-*N*-methyl-*p*-toluenesulfonate (**13**) [21] are reagents reported to be useful for fluorination of enol acetates and carbanions, respectively. The low conversions with anisole even at elevated temperatures illustrate the balance between reactivity and selectivity.

Thus, taking into account factors such as reagent stability, cost and availability, Selectfluor® was chosen as being the optimal reagent and by pure serendipity, our initial starting point for this investigation! We did not study the use of this reagent in combination with trifluomethanesulfonic acid as described by Olah and coworkers [22] as that work involved use of a two-fold molar excess of substrate (e.g. anisole) and also suffers from the limitation that the acid itself could induce side-reactions in some cases.

We have applied the microwave technique to the direct fluorination of more complex materials which might be of use in agrochemical discovery programmes. In a typical example the fluorination of a non-commercial pyrethroid insecticide (**14**) [23] with one equivalent of Selectfluor®, in MeCN at 150 °C for 20 min in a microwave reactor gave as

Table 3
Fluorination of anisole with commercially-available reagents

Reagent	(3) (%)	(4) (%)	(5) (%)	(6) (%)	Recovery (%)	Yield (%)
Selectfluor® (**1**)	26	18	12	2	58	32 (43)
Accufluor® (**2**)	7	24	15	3	48	42 (45)
1,1-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (**7**)	9	10	8	3	30	21 (23)
N-Fluoropyridinium triflate (**8**)	73	1	1	0	75	2 (7)
N-Fluoro-2,4-6-trimethylpyridinium triflate (**9**)	100	0	0	0	100	0
N-Fluorobenzenesulphonimide (**10**)	79	2	2	0	83	4 (19)
2,3-Dihydro-3,3-dimethyl-2-fluoro-1,2-benzisothiazole-1,2-dioxide (**11**)	100	0	0	0	100	0
N-Fluoropyridinium pyridine heptafluorodiborate (**12**)	84	1	1	0	85	1 (13)
N-Fluoro-*N*-methyl-*p*-toluenesulfonate (**13**)	100	0	0	0	100	0

the major isolable product (**15**) (14% yield) after preparative HPLC. The position of fluorine incorporation into (**14**) was determined by *n*Oe and HMBC NMR experiments and a consideration of fluorine couplings in the ^{1}H NMR spectra.

3. Conclusions

We have shown that microwave conditions are readily applicable to the fluorination of aromatic molecules, when a suitable electrophilic fluorination agent is used such as Selectfluor® (**1**) or Accufluor® (**2**). It has been further demonstrated that it is possible to use these conditions to rapidly fluorinate quite complex molecules and isolate novel products in useful quantities.

4. Experimental

4.1. General experimental procedures

Caution: Although we have conducted these experiments many times at the scales reported and no uncontrolled exothermic events or explosions have been observed, care is advised when undertaking this procedure, due to the potential thermal instability of Selectfluor® [13,14].

All Sure-seal®solvents and starting materials (with the exception of (**14**)) are commercially available and were used as received, without further drying or purification. EMRYS CREATOR or EMRYS SYNTHESISER microwave reactors from Smith Personal Chemistry were used to perform the reactions. GC analysis was carried out using an Agilent 6890 GC with FID detector. An Restek RTX200 capillary column was used to effect separation of the components. A typical thermal program was 50 °C (isocratic, 2 min) 50–250 °C (ramp, 15 °C/min). HPLC purification was undertaken using a Varian Prostar HPLC system, fitted with a Varian DYNAMAX microsorb 100-8, normal phase column under isocratic conditions. NMR was carried out using either a Varian Inova 400 or Varian Inova 500 with TMS as an internal standard. HRMS was undertaken using a Joel GC-Mate II mass spectrometer.

4.2. Analysis procedures

(a) The reaction mixture was diluted with EtOAc (to 5 mL) in a volumetric flask and 2-fluoro-biphenyl (5 mg) was added as a standard. Identification of the products was by GC retention time with comparison to commercial samples. Quantification of the materials in the reaction mixture was achieved by integration of the GC trace and calculated against the standard added to the sample.

(b) The reaction mixture was diluted with EtOAc (to 5 mL) in a volumetric flask and 2-fluoro-biphenyl (5 mg) was added as a standard. Identification of the products was by ^{19}F NMR using the data published by Laali and Borodkin [15] in order to determine which isomers were formed. Integration of these signals gave a rough quantification of the new products. Absolute quantification of the materials in the reaction mixture was achieved by integration of the GC trace, comparison with the ^{19}F NMR integration data and calculation against the standard added to the sample.

4.3. General procedure for microwave fluorination

To a 5 mL microwave tube, charged with Selectfluor® (178 mg, 0.5 mmol) was added substrate (0.5 mmol). Acetonitrile (2.5 mL) was added and the tube capped. The reaction was then irradiated to heat it to 150 °C in the microwave cavity for the appropriate length of time. The readings from the temperature, pressure and power sensors of the EMRYS CREATOR showed no unexpected fluctuations for the fluorination reactions.

4.4. Fluorination of (**14**)

To a 5 mL microwave tube, charged with Selectfluor® (178 mg, 0.5 mmol) was added (**14**) (132 mg, 0.5 mmol). Acetonitrile (2.0 mL) was added and the tube capped. The reaction was then irradiated to heat it to 150 °C in the microwave cavity (at no point did the pressure inside the tube exceed 16 atm). After 20 min, the reaction mixture was cooled to ambient and analysed by GC–MS. The mixture was concentrated in vacuo and the resulting solid triturated with dichloromethane (3 × 10 mL). The combined supernatant was concentrated in vacuo and purified via preparative HPLC (isocratic 9:1 hexane/ethyl acetate), giving a 1:1 mixture of (*R*) and (*S*)-α-cyano-4-fluoro-3-(2-fluorophenoxy)-benzyl (*Z*)-(1R,3R)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate (**15**) (34 mg oil, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) 1.18 (3H, s, CH_3), 1.29 (3H, s, CH_3), 2.00 (1H, d, *J* 8.0, $Cl(CF_3)C{=}CHCH$), 2.28 (1H, t, *J* 8.0, $CHCO_2C$), 6.33 (1H, s, $CHCN$) 6.78 (1H, dd, J_F 9.0, *J* 1.0, $Cl(CF_3)C{=}CHCH$), 6.90–7.30 (7H, m, Ar–H); ^{13}C (100 MHz, $CDCl_3$) 14.6, 28.0, 29.8, 31.6, 31.8, 61.9, 115.5, 117.3 (d, J_F 18.5), 118.7, 120.9, 123.0 (q, J_F 37.5), 123.8 (d, J_F 7.0), 124.9 (d, J_F 4.5), 125.7 (d, J_F 7.0), 128.6 (d, J_F 5.0), 129.3, 142.7 (d, J_F 10.5), 145.0 (d, J_F 11.5), 152.3, 152.8, 154.8, 155.4, 186.1; ^{19}F NMR (100 MHz, $CDCl_3$) −68.76 (CF_3), −128.20, −130.95 (Ar–F); *m/z* (GC–MS, CI) 486 $[MH]^+$ (20), 315 (10), 225 (100); HRMS (EI) $C_{23}H_{17}O_3NClF_5$ requires 485.0818 found 485.0826 (+1.8 ppm).

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