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Microwave assisted fluorination: an improved method for side chain fluorination of substituted 1-arylethanones

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ABSTRACT

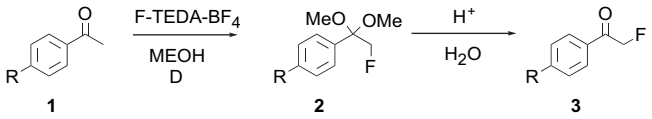
A two-step, one-pot microwave (MW) assisted fluorination of 1-arylethanones to their corresponding 1-aryl-2-fluoroethanones has been developed. The first step utilises Selectfluor™ as a fluorinating agent in methanol forming 1-aryl-2-fluoroethanones and their corresponding dimethyl acetals. In the second step, water is added and Selectfluor™ acts as a Lewis acid in the hydrolytic cleavage of the dimethyl acetals. Compared to the thermal synthesis, the MW assisted method leads to a reduction in reaction time both in the fluorination and for the dimethyl acetal cleavage. Moreover, the one-pot procedure reduces reagent and solvent consumption. The method is best suited for the preparation of 1-aryl-2-fluoroethanones containing substituents that deactivates electrophilic aromatic substitution, however highly electron deficient ketones such as 1-(3,5-dinitrophenyl)ethanone reacts more slowly. Reactions using electron rich aromatic ketones had a low regioselectivity, and also produced fluoroaromatic products.

1. Introduction

Microwave irradiation (MW) is a powerful and easily controllable heating source. For a number of reactions, especially those involving polar transition states, significant rate acceleration can be achieved compared to conventional heating.[1–4]

The use of microwaves has also been applied in various forms of fluorination.[5–13] Selectfluor™ (F-TEDA-BF_4) is a relatively stable electrophilic fluorinating agent,[14] and microwave assisted reactions on 1,3-dicarbonyl compounds,[13] aromatic compounds,[5] and 1-aryl-1-nitromethanes,[11] have been reported. Moreover, F-TEDA-BF_4 has also been applied as a Lewis acid in MW assisted synthesis.[15]

α-Fluoroacetophenones can be synthesised by nucleophilic displacement,[16–21] electrophilic fluorination of ketones, imines or enamines,[22–30] Friedel/Crafts acylation,[31,32] coupling chemistry,[33] and reaction via diazo ketones.[34,35] However, some of these methods have drawbacks due to the use of hazardous and toxic chemicals or the involvement of unstable intermediate compounds. We have recently compared three methods using conventional heating for the preparation of α-fluoroacetophenones.[36] A simple method using only F-TEDA-BF_4 in methanol enabled acetophenones to be fluorinated in decent yields. The method consists of two steps; fluorination yielding the target α-fluoroketone, **3**, its dimethyl acetal, **2**, and subsequent hydrolysis to convert **2** into **3**, Scheme 1.



Scheme 1. Fluorination of acetophenones using F-TEDA-BF_4 in methanol.

Although being very simple, an obvious drawback of the thermal method was the prolonged reaction times, especially for substrates containing electron withdrawing substituents. Moreover, several of the dimethyl acetals, **2**, required heating to reflux in the presence of trifluoroacetic acid for several hours for complete conversion to **3**.

To improve the usefulness of the method, we have investigated the use of microwaves to increase the reaction rates and yields in conversion of 1-arylethanones, **1** to the corresponding 1-aryl-2-fluoroethanones, **3**.

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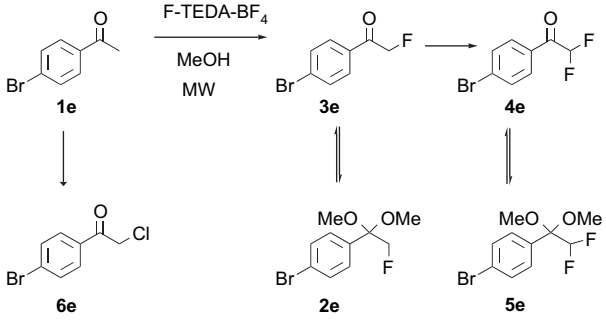
2. Results and discussion

2.1. MW assisted fluorination: solvent, effect (*W*) and reaction time

The reaction rate in the thermal fluorination of acetophenones using F-TEDA-BF_4 in MeOH was very dependant on the electronic properties of the substituents.[36] Therefore, initial experiments using MW as a heating source were performed using 1-(4-bromophenyl)ethanone (**1e**), which was intermediate with respect to electronic character. An Anton Paar 3000 microwave instrument equipped with a magnetic stirrer device was used. The reactions were performed in sealed Teflon tubes.

Running the reaction at 120 W using two equivalents of F-TEDA-BF_4 in methanol revealed that fluorination took place. However, several other fluorinated compounds and undefined substances were present in the discoloured reaction mixture. ^{1}H NMR spectroscopy was used for the identification of reaction components. The ^{1}H NMR chemical shifts of **1**–**3e** (Scheme 2) were known from a previous study.[36] The presence of 1-(4-bromophenyl)-2,2-difluoroethanone (**4e**) could be confirmed by the characteristic triplet at 6.24 ppm (J_{HF}=53.5 Hz). In addition, a triplet with comparable coupling constant was observed at 5.82 ppm (J_{HF}=55.3 Hz). Analysis after hydrolytic treatment revealed that this substance was converted to **4e**, and was therefore assigned as the dimethyl acetal, **5e**. Trace amounts of 1-(4-bromophenyl)-2-chloroethanone (**6e**),[37] was also observed. It is currently unclear if formation of **6e** is due to impurities in F-TEDA-BF_4 or decomposition reactions leading to electrophilic chlorine sources. A chlorinated by-product has previously been reported in fluorination of thiazole using F-TEDA-BF_4.[38]



Scheme 2. Reaction products after fluorination of **1e** in methanol using F-TEDA-BF_4.

Follow-up experiments revealed a positive effect both on conversion and colour of the reaction mixture when the effect was in the range of 80–100 W. Having found a suitable effect (*W*), the choice of reaction medium was reevaluated. If possible, it would be beneficial to avoid the formation of the intermediate dimethyl acetal, **2e**. Moreover, a change in solvent might affect conversion rates due to temperature effects. The fluorination was performed in six different solvents and reacted for 60 min at 80 W. The degree of conversion and product distribution after fluorination are given in Table 1.

Table 1
The conversion (conv.) and product distribution after fluorination of **1e** in different solvents at 80 W for 60 min

Solvent	Conv.[a] (%)	**1e** (%)	**2e** (%)	**3e** (%)	**4e** (%)	**5e** (%)	**6e** (%)
Acetonitrile	36	64	NA	34	0	0	2
t-BuOH	0	100	—	0	0	—	0
i-PrOH	0	100	—	0	0	—	0
EtOH	12	88	[b]	11	0	[a]	1
MeOH	97	3	30	54	11	5	1
Water	8	92	NA	6	—	—	2

[a] Conversion was measured by ^{1}H NMR spectroscopy.
[b] Ethyl acetals were not observed by ^{1}H NMR spectroscopy.

The degree of conversion was highly dependant on the solvent used. No fluorination was observed in *t*-BuOH or *i*-PrOH, while reactions in water and ethanol gave 8 and 12% conversion respectively. The reaction in acetonitrile gave a 36% conversion, whereas 97% was obtained using methanol as reaction solvent. In addition to the α-fluoroketone, **3e**, and its dimethyl acetal, **2e**, the difluoro-compounds **4e** and **5e** were observed. Although, aliphatic difluorination appeared in methanol, the reaction proceeded much faster than in any of the other solvents tested. One could speculate that methanol shifts the keto/enol equilibrium more to the enol side and that this is the reason for the solvent dependant rate acceleration.

Further experiments were undertaken to study how the effect and reaction time influenced the degree of conversion and product distribution using **1e** as substrate. The effect was varied between 60 and 100 W, and the reaction time was varied between 60 and 100 min. The results are summarised in Table 2.

Table 2
Conversion (conv.) and product distribution after fluorination of **1e** in MeOH varying MW effect (W) and reaction time

Entry	Effect (W)	Time (min)	Conv.[a] (%)	**3e**+**2e** (%)	**4e**+**5e** (%)
1	60	60	65	64	0
2	60	100	91	87	3
3	80	80	>99	87	11
4	100	60	97	89	7
5	100	100	98	85	14

[a] Conversion was measured by ^{1}H NMR spectroscopy.

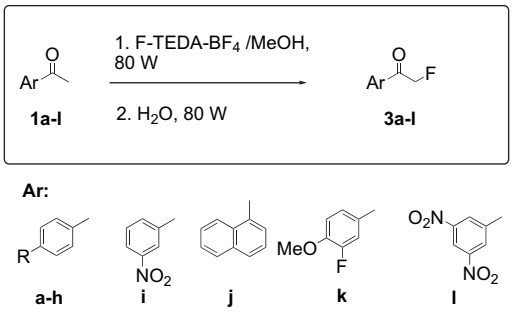
The degree of conversion measured by amount of residual 1-(4-bromophenyl)ethanone (**1e**) versus fluorinated products depended on both effect (*W*) and reaction time. Full conversion was not obtained at 60 W (Entries 1 and 2), due to insufficient reaction time. The incomplete conversion at 100 W was probably due to a thermal decomposition of F-TEDA-BF_4 as it was noted that the reaction mixture turned black. At 80 W, full conversion was obtained without discolouration of the reaction mixture. As full conversion and the absence of coloured by-products allowed for easier product purification, 80 W was selected as the preferred irradiation effect in the fluorinations.

To maximise the yield of the α-fluoroketone **3e**, its dimethyl acetal, **2e** needed to be hydrolysed. F-TEDA-BF_4 has previously been used as a Lewis acid.[15] We therefore tested if cleavage of the dimethyl acetal **2e** could be performed by simply adding water to the crude reaction mixture followed by MW irradiation. This proved to be the case, and **2e** was readily cleaved by addition of water and irradiating the reaction mixture at 80 W for 20 min. This enabled the preparation of **3e** using a one-pot two-step procedure.

2.2. Scope and limitations: substrate structure

To investigate the scope and limitations of the method with respect to substrate structure, a series of 1-arylethanones, **1a**–**l**, were fluorinated, see Scheme 3.

Both substrates with electron donating and withdrawing substituents were investigated. Compound **1k** was included in the study to investigate if one fluorine atom was sufficient to reduce ring fluorination as compared to **1a**. Compound **1l** was used to investigate the effects of two strong electron withdrawing groups on the fluorination and the hydrolysis steps. Both steps were performed at 80 W, and the reaction time was varied to obtain high conversions. Table 3 summarises the conversions and product distributions after fluorination, the conversions obtained in the hydrolytic step, and the yields for **3a**–**l**. The optimised reaction



R= **a** (OMe), **b** (OBn), **c** (H), **d** (F), **e** (Br), **f** (CF_3), **g** (CN), **h** (NO_2)

Scheme 3. Fluorination of **1a–l** using F-TEDA-BF_4.

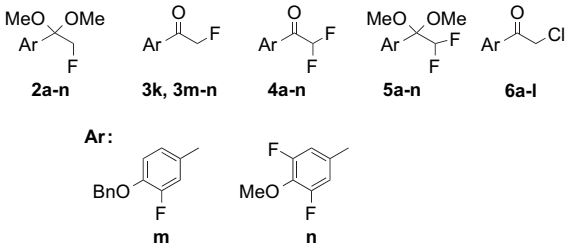


Figure 1. By-products and intermediates observed in preparation of **3a–l**. For structure elements **a–l** see Scheme 3.

times at 80 W for the two steps are given in Table 4 and the structures of the by-products are shown in Figure 1.

The MW assisted fluorination of the electron rich 1-arylethanones **1a–b** (Table 3, Entries 1–2) gave low yields of the target products **3a–b**. This was due to the formation of additional ring fluorinated by-products, **3k** and **3m**, high amounts of α,α-difluoroketones, **4a–b** and their corresponding dimethyl acetals, **5a–b**. Especially difficult was fluorination of 1-acetonaphthone (**1j**) (Entry 3), which led to at least three different α-fluoroketones, their corresponding dimethyl acetals and α,α-difluorides. ^1H and ^{19}F NMR spectroscopic analysis of the crude product mixture suggested that ring fluorination had taken place. These three substrates exemplify limitations of the method in general. Due to the complexity of the reaction mixtures, purifications were not attempted.

In terms of susceptibility towards aromatic fluorination, 1-(3-fluoro-4-methoxyphenyl)ethanone (**1k**), (Entry 4), represents a borderline case. As compared to fluorination of **1a**, the extra *m*-fluorine in **1k** suppressed ring fluorination, and only 5% of **3n** and **4n** was observed. Aliphatic difluorination leading to compound **4k** and **5k** (19%) was however still significant, reducing the isolated yield to 59%.

Fluorination of **1c** and **1d** and subsequent hydrolysis gave 65 and 74% isolated yield of **3c** and **3d** respectively. In the case of **1c**, unidentified by-products were detected, explaining the lower yield.

Table 3
MW assisted fluorination and hydrolysis using F-TEDA-BF_4: conversion (conv.) and product distribution after fluorination, conversion after hydrolysis and yields of **3a–l**. Isolated yields are reported unless otherwise stated. For reaction times see Table 4

Entry	Substrate	Fluorination					Hydrolysis		
		Conv.[a] (%)	2 (%)	3 (%)	4+5 (%)	Others (%)	Conv. (%)	Yield (%)	Product
1	*p*-MeO (**1a**)	>99	11	44	18	27 (**2k**+**3k**)	>99	46[b]	**3a**
2	*p*-BnO (**1b**)	>99	12	46	18	24 (**2m**+**3m**)	>99	46[b]	**3b**
3	1-Naphthyl (**1j**)	90	6	40	nd	Multiple[c]	>99	38[b]	**3j**
4	*m*-F, *p*-OMe (**1k**)	>99	23	53	19	5 (**2n**+**3n**)	>99	59	**3k**
5	H (**1c**)	>99	26	61	12	1 (**6c**)	>99	65	**3c**
6	*p*-F (**1d**)	>99	23	67	9	1 (**6d**)	>99	74	**3d**
7	*p*-Br (**1e**)	>99	24	63	11	1 (**6e**)	>99	81	**3e**
8	*p*-CF_3 (**1f**)	>99	41	52	6	1 (**6f**)	>99	69	**3f**
9	*p*-CN (**1g**)	99	30	62	6	1 (**6g**)	>99	86	**3g**
10	*p*-NO_2 (**1h**)	>99	70	24	5	<1 (**6h**)	>99	82	**3h**
11	*m*-NO_2 (**1i**)	98	58	36	4	1 (**6i**)	>99	72	**3i**
12	3,5-di-NO_2 (**1l**)	94	88	3	3	3 (**7l**)	97	41	**3l**

[a] Conversion was measured by ^1H NMR spectroscopy.
[b] Reaction yield of α-fluoroketone as quantified by ^1H NMR spectroscopy using 1-(4-methoxyphenyl)ethanone as standard.
[c] Not identified.

Table 4
Comparison of the MW (80 W) and thermal process for the preparation of **3a–l** (reaction time and yield)

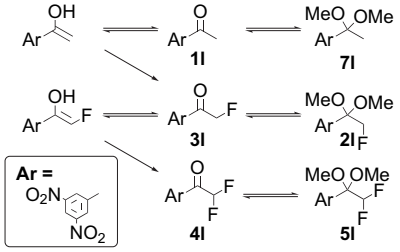
Entry	Substrate	MW			Thermal		
		Rx. time fluorination (min)	Rx. time hydrolysis (min)	Yield (%)	Rx. time fluorination (h)	Rx. time hydrolysis (h)	Yield (%)
1	*p*-MeO (**1a**)	60	15	46[a]	48	1 (rt)	67[b]
2	*p*-BnO (**1b**)	60	15	46[a]	72	1 (rt)	58[b]
3	1-Naphthyl (**1j**)	60	15	38[a]	144	1 (rt)	50[a]
4	*m*-F, *p*-OMe (**1k**)	60	15	59	96	3.5 (rt)	67
5	H (**1c**)	60	15	65	96	3.5 (rt)	66[b]
6	*p*-F (**1d**)	60	20	74	96	3.5 (rt)	25[b]
7	*p*-Br (**1e**)	80	15	81	125	24 (rt)	77[b]
8	*p*-CF_3 (**1f**)	85	25	69	144	20 (reflux)	73[b]
9	*p*-CN (**1g**)	80	30	86	192	20 (reflux)	64[b]
10	*p*-NO_2 (**1h**)	50	30	82	261	20 (reflux)	70[b]
11	*m*-NO_2 (**1i**)	60	30	72	336	20 (reflux)	73
12	3,5-di-NO_2 (**1l**)	120	30	41	500[c]	336[d] (reflux)	39

[a] Reaction yield quantified by ^1H NMR spectroscopy using 1-(4-methoxyphenyl)ethanone as standard.
[b] Results from previous study.[36]
[c] 82% conv.
[d] 63% conv.

In the fluorination of **1d–i** (Entries 5–11), aromatic fluorination was not observed. Moreover, moving down Table 3, as the electronic withdrawing character of the substituents increases, the level of the α,α-difluorides, **4** and **5** observed was also reduced. Higher yields were experienced, and the products could be obtained in 69–86% isolated yield. Electron withdrawing groups on the aromatic ring increased both the amounts and the stability of the dimethyl acetals. As a consequence, the reaction time in the hydrolytic step had to be increased from 15 to 30 min.

Another limitation to the presented method is exemplified by fluorination of 3,5-dinitroacetophenone (**1l**), (Entry 12). This substrate required prolonged reaction time, however, a 94% conversion was obtained by applying 80 W for 2 h.

The main product of the reaction was **2l** (88%) and formation of the dimethyl acetal **7l**,[39] was also noticed (Scheme 4). Such side products were not observed in fluorination of the other substrates.



Scheme 4. Products and assumed reaction intermediates in fluorination of **1l**.

The major challenge in the synthesis of **3l** by this process resides in the hydrolytic step. Somewhat surprisingly, fluorination continued during hydrolysis, resulting in the formation of three difluorinated compounds, including **4l**, **5l** and a unknown compound (δ: 5.79, J_{HF}=55.1 Hz).

The reaction progress for **1l** can be rationalised by referring to Scheme 4. When acetophenones are substituted with electron withdrawing groups, the ketone/dimethyl acetal equilibrium position is shifted towards the dimethyl acetal side.[40] This is especially pronounced in the case of **1l** due to the presence of two nitro groups. It can be assumed that fluorination takes place via the enol form of the ketone, and due to the limited amount of the ketone **1l**, and thereby its enol, a reduction in the reaction rate is experienced. Once formed, the α-fluoroketone, **3l** has an even higher tendency to react with methanol, forming **2l**. As evident from Table 3, the amount of **3l** in the reaction is very low, and further fluorination is therefore difficult. When water is added, the equilibrium position is shifted towards **3l** and its enol form, enabling fluorination to continue. The reason why α,α-difluorination during hydrolysis appears only for **3l** is not understood.

Attempts to fluorinate **1l** in water (80 W, 60 min) gave a complex mixture and a conversion of approximately 30%. The dominating products were **3l**, **4l** and the previous mentioned compound with shift value of 5.79 ppm.

2.3. Comparison of the MW and thermal fluorination methods

A comparison of the MW and the thermal process, with respect to reaction times and yields are shown in Table 4.

The MW assisted reactions benefit from shorter reaction times; fluorination proceeds in 60–120 min, whereas hydrolysis could be performed in 15–30 min. The corresponding thermal fluorinations required several days or weeks for complete conversion. The MW assisted method was inferior to the thermal reaction for the selective aliphatic fluorination of electron rich aromatic ketones (Entries 1–4), due to the formation of high levels of α,α-difluoroketones.

Compared to the thermal process, higher or comparable yields were obtained in the MW assisted fluorination and hydrolysis starting with **1c–i**. The largest difference in yield when comparing the two methods is seen in preparation of **3d** and **3g**.

The dimethyl acetal **2d** was previously found to be highly volatile, and this limited the isolated yield of the reported thermal reaction.[36] The volatility is not a problem in the MW process, as the isolation of **2d** is not required. The lower yield of **3g** in the thermal process is probably due to side reactions at the cyano-group, taking place during the prolonged reaction time.

The MW assisted fluorination of **1l** was hampered by a low reaction rate, and α,α-difluoride formation during hydrolysis. This gave 41% of **3l**. By comparison, the thermal process from **1l** also gave a moderate 39% isolated yield after a total of 5 weeks reaction time.

The reaction rate in the thermal fluorination was correlated with the electronic properties of the substituents. For the MW assisted fluorination, an increase in reaction time was needed for **1e–1g**, compared to **1a–d**. However, this was not seen for the nitro-derivatives, **1h–i**. Nitro groups are known to be efficient absorbers of MW energy, and the observation suggests that specific microwave effects are operating.

The MW process gave a higher ketone to dimethyl acetal ratio and higher amounts of α,α-difluorinated compounds than was the case in the thermal process. It is assumed that fluorination by F-TEDA-BF_4 takes place on the enol form of the ketone, (Scheme 4). As less α-fluoroketones are trapped as dimethyl acetals in the MW process, they are more available for further fluorination. This could explain the elevated levels of the α,α-difluoroketones in the microwave process as compared to the thermal method.

3. Conclusion

A one-pot, two-step MW assisted fluorination of 1-arylethanones has been developed. The main benefit of the MW strategy is a reduction of the reaction time from several days to 1.5–2 h. Moreover, a simplification of the dimethyl acetal cleavage step has been developed, reducing the number of operations, chemical consumption and time.

The method has its main advantage in the fluorination of moderately deactivated acetophenones **1c–i**, leading to the production of the 1-aryl-2-fluoroethanones in 65–86% isolated yield.

Electron rich 1-arylethanones are not selectively fluorinated in the side chain, but also forms fluoroaromatic derivatives. 1-(3-Fluoro-4-methoxyphenyl)ethanone (**1k**) represents a borderline case, where aromatic fluorination is starting to be suppressed.

Another limitation to the fluorination method is in the reaction of 1-arylethanones having two strongly electron withdrawing substituents. Although the fluorination takes place at a reduced rate, the hydrolysis led to the formation of aliphatic α,α-difluorinated compounds, reducing the yield significantly.

4. Experimental

4.1. General

The 1-arylethanones **1a**, **1g–h**, **1l**, and 1,3-dichloro-5,5-dimethylhydantoin were purchased from Fluka. Selectfluor™ (F-TEDA-BF_4), **1c–f**, **1j–k,** and *N*-fluorobisbenzenesulfonimide were from Aldrich. 1-(3-Nitrophenyl)ethanone (**1i**) was from Acros Organics, while 1-(4-bromophenyl)-2-chloroethanone (**6e**) was from Sigma–Aldrich. Methanol was from VWR (HPLC grade, 0.03% water). Column chromatography was performed using silica gel 60A from Fluka, pore size 40–63 μm. 1-(4-(Benzyloxy)phenyl)ethanone (**1b**) was prepared from 4-hydroxyacetophenone using benzyl chloride and potassium carbonate in *N*,*N*-dimethylformamide as solvent.

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^{1}H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. For ^{1}H and ^{13}C NMR chemical shifts are in ppm rel to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. MS (EI/70 eV) Finnigan MAT 95 XL. Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source. Samples were injected into the MS using an Agilent 1100 series HPLC and analysis was performed as a direct injection analysis without any chromatography. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument. The microwave experiments were performed using an Anton Paar 3000 instrument with a magnetic stirrer device.

4.3. General procedure MW assisted fluorination

To a Teflon reaction tube containing a magnetic stirrer bar 1-arylethanone (2.21 mmol), Selectfluor™ (4.42 mmol) and methanol (5 mL) were added. The reaction chamber was sealed and treated at 80 W for the times specified in Table 4. After cooling, water (5 mL) was added and the mixture was hydrolysed at 80 W with the reaction times specified in Table 4. After cooling, water (15 mL) was added and the mixture was extracted with CH_2Cl_2 (4×15 mL). The dichloromethane layer was then washed with brine (15 mL), dried over Na_2SO_4 and evaporated to dryness. The 1-aryl-2-fluoroethanones were purified by the methods specified for each single compound.

4.4. Thermal fluorination in methanol

Thermal fluorination of the 1-arylethanones (1 equiv) in MeOH using F-TEDA-BF_4 (2 equivalents) was performed as described previously.[36]

4.5. 1-Aryl-2-fluoroethanones

*4.5.1. 2-Fluoro-1-(4-methoxyphenyl)ethanone (**3a**)*[22,36]. The identity of compound **3a** was verified by comparison of ^{1}H NMR shifts with a previous study.[36] ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 3H), 5.45 (d, J=47.2, 2H), 6.96 (m, 2H), 7.89 (m, 2H).

*4.5.2. 1-(4-(Benzyloxy)phenyl)-2-fluoroethanone (**3b**)*[36]. The identity of compound **3b** was verified by comparison of ^{1}H NMR shifts with a previous study.[36] ^{1}H NMR ($CDCl_3$) δ: 5.14 (s, 2H), 5.46 (d, J=47.0, 2H), 7.02–4.04 (m, 2H), 7.36–7.43 (m, 5H) and 7.87–7.89 (m, 2H).

*4.5.3. 2-Fluoro-1-phenylethanone (**3c**)*[19,36]. Compound **3c** was prepared as described in Section 4.3 starting with **1c** (265 mg, 2.21 mmol). Fluorination was performed for 60 min, and hydrolysis was done in 15 min. Purification by silica gel chromatography (pentane/EtOAc, 85/15) gave 198 mg (1.43 mmol, 65%) of **3c** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 5.53 (d, J=47.0, 2H), 7.50 (m, 2H), 7.63 (m, 1H), 7.90 (m, 2H).

*4.5.4. 2-Fluoro-1-(4-fluorophenylethanone) (**3d**)*[25,36]. Compound **3d** was prepared as described in Section 4.3 starting with **1d** (305 mg, 2.21 mmol). Fluorination was performed for 60 min, and hydrolysis was done in 20 min. Purification by silica gel chromatography (pentane/EtOAc, 85/15) gave 255 mg (1.63 mmol, 74%) of **3d** as a white solid mp 49–51 °C. ^{1}H NMR ($CDCl_3$) δ: 5.49 (d, J=46.9, 2H), 7.15–7.21 (m, 2H) and 7.83–7.98 (m, 2H).

*4.5.5. 1-(4-Bromophenyl)-2-fluoroethanone (**3e**)*[34,36]. Compound **3e** was prepared as described in Section 4.3 starting with **1e** (440 mg, 2.21 mmol). Fluorination was performed for 80 min, and hydrolysis was done in 15 min. Purification by silica gel chromatography (pentane/EtOAc, 85/15) gave 387 mg (1.78 mmol, 81%) of **3e** as a white solid mp 72–73 °C. ^{1}H NMR ($CDCl_3$) δ: 5.46 (d, J=46.9, 2H), 7.64 (m, 2H) and 7.77 (m, 2H).

*4.5.6. 2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethanone (**3f**)*[36]. Compound **3f** was prepared as described in Section 4.3 starting with **1f** (415 mg, 2.21 mmol). Fluorination was performed for 85 min, and hydrolysis was done in 25 min. Purification by silica gel chromatography (CH_2Cl_2) gave 312 mg (1.52 mmol, 69%) of **3f** as a white solid mp 36–37 °C. ^{1}H NMR ($CDCl_3$) δ: 5.52 (d, J=46.8, 2H), 7.77 (m, 2H), 8.03 (m, 2H).

*4.5.7. 4-(2-Fluoroacetyl)benzonitrile (**3g**)*[36]. Compound **3g** was prepared as described in Section 4.3 starting with **1g** (321 mg, 2.21 mmol), Fluorination was performed for 80 min, and hydrolysis was done in 30 min. Purification by silica gel chromatography (pentane/acetone, 7/3) gave 312 mg (1.90 mmol, 86%) of **3g** as a white solid mp 104–105 °C. ^{1}H NMR ($CDCl_3$) δ: 5.51 (d, J=46.8, 2H), 7.81 (m, 2H) and 8.02 (m, 2H).

*4.5.8. 2-Fluoro-1-(4-nitrophenyl)ethanone (**3h**)*[36]. Compound **3h** was prepared as described in Section 4.3 starting with **1h** (365 mg, 2.21 mmol), Fluorination was performed for 50 min, and hydrolysis was done in 30 min. Purification by silica gel chromatography (pentane/acetone, 7/3) gave 333 mg (1.81 mmol, 82%) of **3h** as a white solid mp 96–97 °C. ^{1}H NMR ($CDCl_3$) δ: 5.55 (d, J=46.8, 2H), 8.11 (m, 2H) and 8.35 (m, 2H).

*4.5.9. 2-Fluoro-1-(3-nitrophenyl)ethanone (**3i**)*[41]. Compound **3h** was prepared as described in Section 4.3 starting with **1h** (370 mg, 2.21 mmol), Fluorination was performed for 60 min, and hydrolysis was done in 30 min. Purification by crystallisation from ethanol gave 293 mg (1.60 mmol, 72%) of **3h** as a white solid mp 83–84 °C. ^{1}H NMR ($CDCl_3$) δ: 5.55 (d, J=46.7, 2H), 7.72–7.77 (m, 1H), 8.27–8.29 (m, 1H), 8.48–8.51 (m, 1H), 8.75–8.76 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 83.9 (d, J=184.7), 123.1 (d, J=3.9), 128.3, 130.3, 133.8 (d, J=3.5), 135.0 (d, J=1.4), 148.5, 192.0 (d, J=17.0). ^{19}F NMR ($CDCl_3$) δ: −229.7 (t, J=46.8). IR (neat, cm^{-1}): 3101, 1712, 1630, 1537, 1438, 1239, 1080, 1021, 901, 730.

*4.5.10. 2-Fluoro-1-(naphthalen-1-yl)ethanone (**3j**)*[42]. For identification purpose, compound **3j** was synthesised from **1j** (3.64 g, 21 mmol) via the trimethylsilyl enol ether as described by Fuglseth et al.[36] The product was purified by silica gel column chromatography (CH_2Cl_2) giving an oil. A following crystallisation from EtOAc/pentane yielded 1.10 g (5.83 mmol, 29%) of a white solid mp 44–45 °C. The ^{1}H, ^{13}C and ^{19}F NMR spectra corresponded with that reported.[42] ^{1}H NMR ($CDCl_3$) δ: 5.60 (d, J=47.2, 2H), 7.50–7.61 (m, 2H), 7.65 (m, 1H), 7.80 (m, 1H), 7.89 (m, 1H), 8.05 (d, J=8.3, 1H), 8.71 (m, 1H).

*4.5.11. 2-Fluoro-1-(3-fluoro-4-methoxyphenyl)ethanone (**3k**)*[22,36]. Compound **3k** was prepared as described in Section 4.3 starting with **1k** (370 mg, 2.21 mmol). Fluorination was performed for 60 min, and hydrolysis was done in 15 min. Purification by silica gel column chromatography (pentane/EtOAc, 5/2) gave 241 mg (1.30 mmol, 59%) of **3k** as a white solid mp 84–85 °C. ^{1}H NMR ($CDCl_3$) δ: 3.97 (s, 3H), 5.44 (d, J=47.0, 2H), 7.04 (m, 1H), 7.70 (m, 2H).

*4.5.12. 1-(3,5-Dinitrophenyl)-2-fluoroethanone (**3l**).* Compound **3l** was prepared as described in Section 4.3 starting with **1l** (464 mg,

2.21 mmol). Fluorination was performed for 120 min, and hydrolysis was done in 30 min. Compound **3l** was purified by crystallisation from chloroform giving 204 mg (0.89 mmol, 41%) of a white solid, mp 111–112 °C. ^{1}H NMR ($CDCl_3$) δ: 5.55 (d, J=47.0, 2H), 9.04–9.05 (m, 2H), 9.28–9.30 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 84.3 (d, J=186.9), 123.0, 128.3 (d, J=4.9, 2C), 136.5 (d, J=2.0), 149.0 (2C), 190.7 (d, J=18.4). ^{19}F NMR ($CDCl_3$) δ: −227.3 (t, J=46.9). HRMS (ESI): 227.0106 (calcd 227.0110, M−H$^+$). IR (neat, cm^{-1}): 3116, 3084, 2942, 1709, 1612, 1525, 1349, 1230, 1074, 975, 805, 736.

*4.5.13. 1-(3,5-Difluoro-4-methoxyphenyl)-2-fluoroethanone (**3n**).* Compound **3n** was isolated after a thermal fluorination protocol as described previously,[36] starting with **1k** (1.49 mg, 8.84 mmol). Fluorination was performed for 96 h., while hydrolysis in TFA/water/$CHCl_3$ was performed for 3.5 h. The by-product, **3n**, was isolated by silica gel chromatography (pentane/EtOAc, 7/3) giving 14 mg (0.07 mmol, 1%) of a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 4.14 (t, J=1.8, 3H), 5.40 (d, J=46.9, 2H), 7.47–7.52 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 61.7 (t, J=4.2), 83.6 (d, J=184.4), 112.6 (ddd, J=3.9, 7.4, 16.6, 2C), 117.2 (d, J=1.4), 141.6, 154.9 (dd, J=5.7, 256.4, 2C), 190.7 (d, J=16.0). ^{19}F NMR ($CDCl_3$) δ: −127.2 (d, J=8.0), −229.2 (t, J=46.9). HRMS (ESI): 205.0473 (calcd 205.0471, M+H$^+$). IR (neat, cm^{-1}): 2946, 2847, 1708, 1517, 1432, 1330, 1081, 1040, 992, 707.

4.6. 1-Aryl-1,1-dimethoxyethylfluorids (2)

Seven 1-aryl-2,2-dimethoxyethylfluorides were characterised in the previous study.[36] The identity of the dimethyl acetals **2d** and **2n** was assumed from their ^{1}H NMR shifts and coupling constants, and their conversion to the corresponding 1-aryl-2-fluoroethanones by hydrolysis.

*4.6.1. 1-(2-Fluoro-1,1-dimethoxyethyl)-3-nitrobenzene (**2i**).* Compound **2i** was synthesised from **1i** (370 mg, 2.21 mmol) by MW fluorination at 80 W for 60 min, omitting the hydrolytic step. Purification by silica gel chromatography (pentane/acetone, 7/3), gave 137 mg (0.60 mmol, 27%) of a slightly yellowish solid, mp 57–59 °C. ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 6H), 4.52 (d, J=47.0, 2H), 7.58 (m, 1H), 7.86 (m, 1H), 8.22 (m, 1H) and 8.42 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 49.3 (2C), 82.5 (d, J=178.4), 99.9 (d, J=20.8), 122.8 (d, J=1.1), 123.6, 129.3, 133.5 (d, J=1.1), 140.8, 148.5. ^{19}F NMR ($CDCl_3$) δ: −231.7 (t, J=47.0). HRMS (ESI): 252.0643 (calcd 252.0648, M+Na$^+$). IR (neat, cm^{-1}): 3097, 1543, 1348, 1070, 730, 695.

*4.6.2. 1-(2-Fluoro-1,1-dimethoxyethyl)-3,5-dinitrobenzene (**2l**).* Compound **2l** was synthesised from **1l** (464 mg, 2.21 mmol) by MW fluorination at 80 W for 120 min, omitting the hydrolytic step. Purification by silica gel chromatography (pentane/acetone, 7/3), gave 157 mg (0.57 mmol, 26%) of a slightly yellowish solid, mp 87–91 °C. ^{1}H NMR ($CDCl_3$) δ: 3.34 (s, 6H), 4.56 (d, J=46.8, 2H), 8.72 (d, J=2.1, 2H) and 9.05 (t, J=2.1, 1H). ^{13}C NMR ($CDCl_3$) δ: 49.5 (2C), 81.7 (d, J=178.7), 99.6 (d, J=21.2), 119.0, 127.9 (d, J=1.1, 2C), 143.5, 148.6 (2C). ^{19}F NMR ($CDCl_3$) δ: −232.2 (t, J=46.9). IR (neat, cm^{-1}): 3086, 1528, 1347, 1064, 703.

4.7. 1-Aryl-2,2-difluoroketones (4)

The ^{1}H NMR chemical shift and the coupling constants of the difluoromethylene groups in the α,α-difluoroketones were compared by that reported previously for **4a**,[29,43] **4c**,[29] **4e**,[43] and **4h**.[28] Selected compounds were isolated or synthesised. The compounds **4i** and **4j** could not be isolated in a sufficiently pure form for characterisation.

*4.7.1. 2,2-Difluoro-1-phenylethanone (**4c**)[29].* Compound **4c** was prepared as described for **3c** using MW heating. Purification by silica gel chromatography (pentane/acetone, 85/15) gave 41 mg (0.26 mmol, 12%) of **4c** as an oil. ^{1}H NMR data corresponded with that reported previously.[29] ^{1}H NMR ($CDCl_3$) δ: 6.29 (t, J=53.6, 1H), 7.54 (m, 2H), 7.68 (m, 1H), 8.08 (m, 2H).

*4.7.2. 2,2-Difluoro-1-(4-fluorophenyl)ethanone (**4d**)[44].* Compound **4d** was prepared as described for **3d** using MW heating. Purification by silica gel chromatography (pentane/acetone, 85/15) gave 63 mg (0.36 mmol, 16%) of **4d** as an oil. ^{1}H NMR ($CDCl_3$) δ: 6.24 (t, J=53.6, 1H), 7.21 (m, 2H) and 8.13 (m, 2H).

*4.7.3. 1-(4-Bromophenyl)-2,2-difluoroethanone (**4e**)[43].* Compound **4e** was prepared as described for **3e** using MW heating. Purification by silica gel chromatography (pentane/acetone, 85/15) gave 85 mg (0.36 mmol, 16%) of **4e** as an oil. ^{1}H NMR data corresponded with that reported previously.[43] ^{1}H NMR ($CDCl_3$) δ: 6.24 (t, J=53.5, 1H), 7.69 (m, 2H), 7.95 (m, 2H).

*4.7.4. 2,2-Difluoro-1-(4-trifluoromethylphenyl)ethanone (**4f**).* Compound **4f** was prepared as described for **3f** using MW heating. Purification by silica gel chromatography (CH_2Cl_2) gave 87 mg (0.38 mmol, 17%) of **4f** as an oil. ^{1}H NMR ($CDCl_3$) δ: 6.27 (t, J=53.4, 1H), 7.81 (m, 2H) and 8.21 (m, 2H).

*4.7.5. 2,2-Difluoro-1-(4-nitrophenyl)ethanone (**4h**)[28].* Compound **4h** was synthesised as described by Peng et al.[28] starting with **1h** (2.07 g, 12.53 mmol). The crude product obtained (1.65 g, contaminated with **3h**) had an ^{1}H NMR spectra, which corresponded well with that reported. ^{1}H NMR ($CDCl_3$) δ: 6.28 (t, J=53.3, 1H), 8.27 (m, 2H), 8.39 (m, 2H).

*4.7.6. 2,2-Difluoro-1-(naphthalen-1-yl)ethanone (**4j**)[42].* Compound **4j** was synthesised based on the method reported by Verniest et al.[30] starting with **1j** (2.30 g. 13.54 mmol). Compound **1j** was first converted to its corresponding methyl imine, followed by fluorination using *N*-fluorobisbenzenesulfonimide. The difluorinated imine formed was hydrolysed using HCl. This gave after purification by silica gel column chromatography (CH_2Cl_2) 1.34 g, (6.50 mmol, 48%) of a pale yellow oil. The ^{1}H, ^{13}C and ^{19}F NMR spectra corresponded with that reported.[42] ^{1}H NMR ($CDCl_3$) δ: 6.42 (t, J=53.9, 1H), 7.54–7.63 (m, 3H), 7.68 (m, 1H), 7.91 (d, J=8.0, 1H), 8.14 (d, J=8.0, 1H), 8.19 (m, 1H), 8.85 (d, J=8.0, 1H).

4.8. 1-Aryl-2-chloroethanones (6)

Trace impurities of 1-aryl-2-chloroethanoes were observed after most fluorinations. The identity of selected compounds was verified by isolation or synthesis.

*4.8.1. 1-(4-(Benzyloxy)phenyl)-2-chloroethanone (**6b**)[45].* 1-(4-Benzyloxyphenyl)ethanone (**1b**) (5.49 g, 19.0 mmol) and *p*-TsOH (2.31 g, 12.1 mmol) were suspended in methanol (500 mL) at 40 °C. Then 1,3-dichloro-5,5-dimethylhydantoin (3.59 g, 18.2 mmol) was added in portions over 1 h, followed by agitation of the reaction mixture at 40 °C for 22 h. Methanol was then distilled off until crystallisation started, followed by slow addition of water (200 mL). The suspension formed was then stirred for 45 min followed by isolation of the solid material. The crude product was recrystallised from EtOAc/ethanol. This gave 4.03 g (63%) of a white solid, mp 111–112 °C (Lit.[45] 109–110 °C). ^{1}H and ^{13}C NMR spectra corresponded with that reported.[45] ^{1}H NMR ($CHCl_3$) δ: 4.62 (s, 2H), 5.13 (s, 2H), 7.01 (m, 2H), 7.30–7.42 (m, 5H), 7.92 (m, 2H).

*4.8.2. 1-(4-Bromophenyl)-2-chloroethanone (**6e**)[37].* The identity of **6e** was verified by HPLC co-eluation with a commercial sample of **6e**. Column: Symmetry C8 3.5 μm, 4.6×150 mm, (Waters Corp.,

Massachusetts, USA); gradient elution starting with H_2O/acetonitrile/diethylamine (98/2/0.1, vol %), to H_2O/acetonitrile/diethylamine (30/70/0.1, vol%) after 70 min; flow rate: 1.0 mL/min; detection at 220 nm, retention time **6e**: 57.3 min.

*4.8.3. 2-Chloro-1-(trifluoromethylphenyl)ethanone (**6f**)*[46]. Following a thermal fluorination of **1f** (1.58 g, 8.84 mmol) in methanol using F-TEDA-BF_4, and acetal cleavage using trifluoroacetic acid as described previously,[36] 9 mg (0.04 mmole, 0.5%) of **6f** as an oil was isolated by silica gel column chromatography (CH_2Cl_2). ^{1}H NMR data in DMSO-d_6 corresponded with that reported.[46] ^{1}H NMR (DMSO-d_6) δ: 5.28 (s, 2H), 7.94 (m, 2H), 8.17 (m, 2H).

*4.8.4. 2-Chloro-1-(4-nitrophenyl)ethanone (**6h**)*[37]. Compound **6h** were obtained after a thermal fluorination a of **1h** (2.92 g, 17.68 mmol) in methanol for 11 days, followed by acetal cleavage using hydrochloric acid (10%, 20 mL) in THF (80 mL) at 65 °C overnight. After work-up, the resulting solid was crystallised from $CHCl_3$. The resulting mother liquor was then purified by silica gel chromatography ($CHCl_3$) yielding 30 mg (0.02 mmol, 1%) of an off-white solid, mp 87–91 °C. ^{1}H and ^{13}C NMR data corresponded with that reported.[47] ^{1}H NMR ($CDCl_3$) δ: 4.72 (s, 2H), 8.15 (m, 2H), 8.36 (m, 2H).

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