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Electrophilic and nucleophilic side chain fluorination of *para*-substituted acetophenones

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ABSTRACT

para-Substituted α-fluoroacetophenones have been synthesised by three different routes. Electrophilic fluorination of trimethylsilyl enol ethers of acetophenones using Selectfluor (F–TEDA–BF_4, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate)) gave high to moderate yield depending on the electronic properties of the substituents. F–TEDA–BF_4 mediated fluorination of acetophenones in methanol resulted in a mixture of α-fluoroacetophenones and the corresponding 2-fluoro-1,1-dimethyl acetals. The dimethyl acetals were hydrolysed using trifluoroacetic acid in water to maximise the yield of the product. Nucleophilic fluorination of α-bromoacetophenones using tetrabutylammonium hydrogen bifluoride (TBABF) led to moderate yield when having electron-donating substituents, whereas low yields were experienced when more electron-withdrawing substituents were introduced.

1. Introduction

The importance of fluorinated compounds in pharmaceuticals, agrochemicals and material sciences has been thoroughly recognised.[1–5] As a consequence fluorinated building blocks are required. α-Fluoroacetophenones can give access to a number of interesting molecules by reaction at the keto-group, the α-carbon or the aromatic ring. Examples include synthesis of fluorinated tetralones,[6] pyrozoles[7] and thiadiazoles.[8] α-Fluoroacetophenones are also suitable starting materials for fluorochemicals such as 1,1,2-trifluoroethyl aryl ethers,[9] 1,2-difluoroethylaryls[10] and 1,1,2-trifluoroethylaryls.[11]

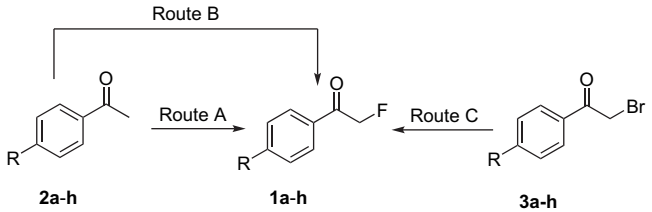
Various methods can be used for synthesis of α-fluoroacetophenones, including nucleophilic displacement,[11–16] electrophilic fluorination,[7,17–21] Friedel–Crafts chemistry,[22,23] coupling chemistry[24] and reaction via diazo ketones.[25,26] Some of these methods have drawbacks due to the use of hazardous and toxic chemicals.

Being in need of a series of α-fluoroacetophenones, it was recognised that the literature mainly covers reactions towards the parent compound 2-fluoro-1-phenylethanone, and no systematic study on the effect of substrate structure on yield had been performed. Therefore, the aim of the work was to compare the usefulness of two electrophilic and one nucleophilic strategies for the preparation of eight different *para*-substituted α-fluoroacetophenones. Targeting nonhazardous procedures, Selectfluor (F–TEDA–BF_4) and tetrabutylammonium hydrogen bifluoride (TBABF) were selected as fluorination reagents. F–TEDA–BF_4 is a stable crystalline solid with low hydroscopicity and toxicity, suited for safe fluorination.[27] TBABF is a nucleophilic fluorine source, claimed to be noncorrosive, possessing good solubility properties, and having a high thermal stability.[12]

2. Results and discussion

2.1. Comparison of the routes

The three routes investigated for the synthesis of α-fluoroacetophenones, **1a**–**h**, are shown in Scheme 1.



Scheme 1. Route A: (1) Base/TMSCl, (2) F–TEDA–BF_4. Route B: (1) F–TEDA–BF_4, (2) TFA. Route C: TBABF. R=OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**) and NO_2 (**h**).

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In route A, acetophenones were converted to the corresponding trimethylsilyl enol ethers, and reacted with F–TEDA–BF_4. The fluorination was performed in acetonitrile at room temperature. In route B,[7,17] electrophilic fluorination of the acetophenones, **2a**–**h**, was performed using 2 equiv of F–TEDA–BF_4 in refluxing methanol. The reaction yielded the fluorinated ketones **1a**–**h** and their corresponding 2-fluoro-1,1-dimethyl acetals. Hydrolysis under acidic conditions was required to convert the acetals to the α-fluoroacetophenones, **1a**–**h**. For the nucleophilic approach (route C), the α-bromoacetophenones, **3a**–**h**, were reacted with 2 equiv of TBABF in refluxing THF. The isolated yields for the three strategies are summarised in Table 1.

Table 1
Isolated yields for the routes A–C

R	Product	Isolated yield (%)		
		Route A	Route B	Route C
OMe	**1a**	91	67	48
OBn	**1b**	89	58	51
H	**1c**	76	66	42
F	**1d**	74	25	36
Br	**1e**	69	77	33
CF_3	**1f**	69	73	26
CN	**1g**	55	64	20
NO_2	**1h**	44	70	20

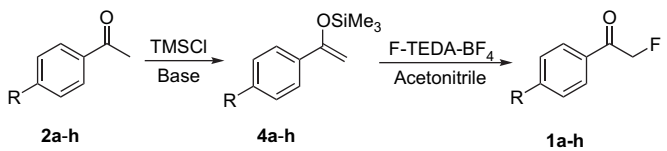
Electrophilic fluorination via the trimethylsilyl enol ethers (route A) provided on average the highest yield. The process was especially suited for substrates bearing electron-donating substituents. A decrease in yield was observed as more electron-withdrawing groups were introduced, and only a moderate 44% yield was obtained for the 4-nitro derivative, **1h**.

Fluorination of acetophenones in methanol (route B) gave yields in the range of 25–77%. Fluorination of **2a**–**b** also led to ring fluorinated by-products, which complicated the purification step. Of the methods tested, route B gave the highest yields of **1e**–**h**.

Nucleophilic fluorination of **3a**–**h** using TBABF (route C) gave moderate to low yield, depending on substrate structure. The best yields for route C were obtained when reacting α-bromoacetophenones having electron-donating substituents, whereas for substrates bearing electron-withdrawing substituents low yields were experienced.

2.2. Electrophilic fluorination via trimethylsilyl enol ethers (route A)

In the first step, the acetophenones (**2a**–**h**) were converted to the trimethylsilyl enol ethers **4a**–**h**, Scheme 2. For preparation of **4a**–**g**, lithium hexamethyldisilazane (LiHMDS) and trimethylsilyl chloride (TMSCl) were used, giving a conversion of >98%. Compound **4h** proved to be more difficult to prepare in decent purity by this method. Changing the base to DBU improved the synthesis, and a conversion of 95% could be obtained.

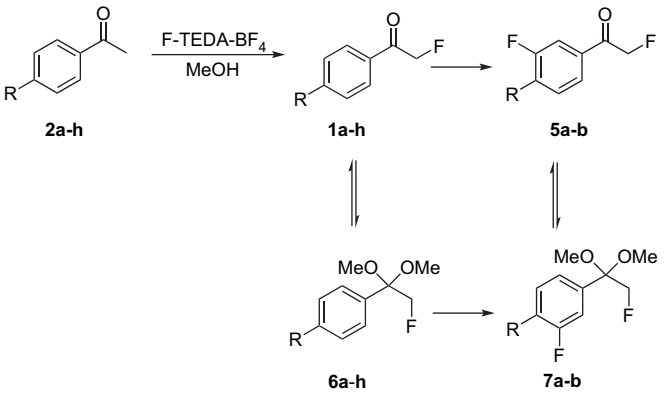


Scheme 2. Synthesis of **1a**–**h** via the trimethylsilyl enol ethers, **4a**–**h**, using F–TEDA–BF_4.

The crude trimethylsilyl enol ethers, **4a**–**h**, were treated with F–TEDA–BF_4 at room temperature in acetonitrile. The reaction progress was monitored by ^{1}H NMR spectroscopy. Some reactions failed to go to completion, but addition of 0.1–0.3 additional equivalents of F–TEDA–BF_4 allowed for full conversion (>98%). Of the substrates tested, only fluorination of **4h** failed to reach full conversion after additional F–TEDA–BF_4 had been added. The highest conversion obtained for **1h** via route A was 91%.

2.3. Electrophilic fluorination in methanol (route B)

Treating the acetophenones, **2a**–**h**, with 2 equiv of F–TEDA–BF_4 in refluxing methanol[7] gave the products **1a**–**h** and the corresponding 2-fluoro-1,1-dimethyl acetals, **6a**–**h**, Scheme 3. For substrates bearing electron-donating substituents, the ring fluorinated ketones, **5a**–**b**, and their 2-fluoro-1,1-dimethyl acetals, **7a**–**b**, were also formed. The chemoselectivity (aliphatic/aromatic) was found to be dependent on the degree of conversion, with higher conversion leading to increased levels of **5a**–**b** and **7a**–**b**.



Scheme 3. Products formed in fluorination of acetophenones using F–TEDA–BF_4 in methanol.

Table 2 summarises the reaction time, degree of conversion and product distribution for the reactions prior to acetal cleavage. The reaction time varied from 48 h for **2a** to 11 days for **2h**.

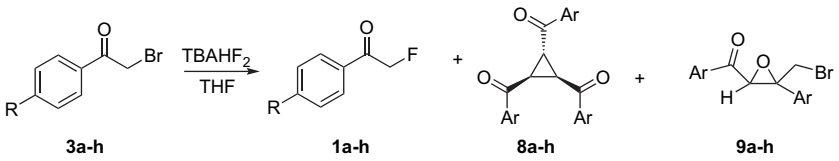
The ketone to dimethyl acetal product ratio depended on substrate structure, the dimethyl acetal form being favoured by electron-withdrawing groups. This is in agreement with ketone–dimethyl acetal equilibrium constants found for acetophenones.[28] ^{1}H NMR spectroscopy also indicated trace amounts of α,α-difluoroacetophenones and α-chloroacetophenones being present at high conversions. The formation of the latter is most likely due to electrophilic chlorine impurities in the commercial reagent.

Treating the ketone/dimethyl acetal mixture under acidic conditions, converted **6a**–**h** and **7a**–**b** to the corresponding α-fluoroacetophenones, **1a**–**h** and **5a**–**b**. The yield of **1a**–**h** varied between 25 and 77%. The low yield in the case of **1d** is explained by the volatility of the intermediate 2-fluoro-1,1-dimethyl acetal, **6d**. A test distillation performed at atmospheric pressure, revealed that both **6d** and **1d** co-distilled with methanol at 66–67 °C.

The hydrolytic stability of the dimethyl acetals was also dependent on the aromatic substituents. Electron-withdrawing

Table 2
Reaction time, conversion and product distribution (^{1}H NMR spectroscopy) for fluorination of acetophenones, **2a**–**h**, using F–TEDA–BF_4 in methanol

Substrate	Reaction time (h)	Conv. (%)	Product distribution (%)			
			1	**5**	**6**	**7**
2a	48	98	67	13	11	7
2b	72	96	57	6	24	9
2c	96	98	36	0	62	0
2d	96	99	38	0	61	0
2e	125	98	26	0	72	0
2f	144	99	7	0	92	0
2g	192	99	13	0	86	0
2h	261	99	7	0	92	0



Scheme 4. Synthesis of α-fluoroketones, **1a–h**, via α-bromoketones **3a–h**, using TBABF.

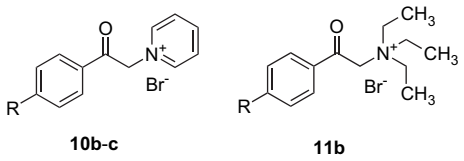
groups increased the stability. Compound **6h** proved to be particularly stable and could not be cleaved by several protocols.[29–31] However, refluxing with 10% aqueous hydrochloric acid in THF, or trifluoroacetic acid/water/chloroform,[32] provided full conversion within 20 h. The use of HCl had the drawback of formation of small amounts of the corresponding α-chloroacetophenone. The mechanistic rational behind this transformation has not been investigated.

2.4. Nucleophilic displacement (route C)

The yield of the nucleophilic displacement reaction using TBABF depended on the aromatic ring substituents. Moderate outcome was observed for substrates having electron-donating groups, whereas only 20% isolated yield was obtained for **1g–h**. The decrease in reaction yield through the series parallels the increasing electron-withdrawing property and acidity of the acetophenones.[33] The main by-products in these reactions were *trans*-1,2,3-tri-(benzoyl)cyclopropanes, **8a–h**, Scheme 4.

In the case of **3c–e**, ca. 20% of the substrates were consumed in this side reaction. Compounds **8c–e** were isolated and characterised. The stereochemistry of **8c–e** was evident from the ^{1}H NMR spectra, which contained a one proton triplet at ca. 4.2 ppm and a two proton doublet at ca. 3.7 ppm, both with a coupling constant of ca. 5.6 Hz. These compounds are most likely formed via the *trans*-1,2-dibenzoylethylenes, by a cycloaddition reaction of ionic character.[34,35] ^{1}H NMR spectroscopy also indicated compounds **9a–h**, products of Darzen-type condensations,[36–38] to be formed under these conditions.

Pyridine and triethylamine have previously been used in fluorinations of α-bromoacetophenones using TBABF.[15,39] The method was tested in fluorination of **3b** using both pyridine and triethylamine, and in reaction of **3c** using pyridine. However, this led to further loss in yield due to formation of compounds **10b**, **11b** and **10c**, Scheme 5.



Scheme 5. By-products caused by pyridine or triethylamine.

3. Conclusion

Using three different methods, eight α-fluoroacetophenones have been prepared. Three of these have previously not been characterised (**1b**, **1f** and **1g**). In general, electrophilic fluorination via the trimethylsilyl enol ethers, **4a–h**, using F–TEDA–BF_4, gave higher yields than that for the other methods tested. The yield depended on the aromatic ring substituents, with substrates bearing electron-donating groups giving higher yield. In contrast to molecular fluorine and trifluoromethyl hypofluorite,[18,20] the use of F–TEDA–BF_4 enables the fluorination to take place at room temperature in conventional media. Fluorination of acetophenones with F–TEDA–BF_4 in methanol gave the α-fluoroacetophenones, **1a–h**, and the corresponding 2-fluoro-1,1-dimethyl acetals, **6a–h**. The dimethyl acetals were hydrolysed to **1a–h** using trifluoroacetic acid. The method is experimentally simple, and the yields were independent of the electronic properties of the aromatic substituents. The protocol suffers from low chemoselectivity for substrates bearing electron-donating groups, prolonged reaction times and the requirement of 2 equiv of F–TEDA–BF_4. However, the method gave the highest yields for compounds **1e–h**. Nucleophilic displacement of α-bromoacetophenones containing electron-donating substituents gave moderate yields. For substrates bearing electron-withdrawing groups, condensation reactions led to complex mixtures and low yields. Compared to the electrophilic fluorinations, this method is of less value.

4. Experimental

4.1. General

The acetophenones **2a**, **2c** and **2f–h**, the α-bromoacetophenones **3a** and **3c** and tetrabutylammonium hydrogen bifluoride (50% solution) were purchased from Fluka. LiHMDS, Selectfluor (F–TEDA–BF_4) and trimethylsilyl chloride were purchased from Aldrich. Column chromatography was performed using silica gel 60A from Fluka, pore size 40–63 μm. 1-(4-Benzyloxyphenyl)ethanone (**2b**) was prepared from 4-hydroxyacetophenone using benzyl chloride and potassium carbonate in *N*,*N*-dimethylformamide as solvent. 1-(4-Fluorophenyl)ethanone (**2d**) was prepared as described by Olah et al.[40] The α-bromoacetophenones **3b** and **3d–h** were prepared by bromination of the corresponding acetophenones using molecular bromine. NMR spectra and high resolution mass spectra were in accordance with proposed structures. Compounds **6b**, **6e–h** and **7b** were isolated by column chromatography after synthesis according to route B (4.41 mmol scale), omitting the hydrolytic step.

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 parts per million relative to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. NMR resonance assignment was aided by the HMBC technique.[41] MS (EI/70 eV): Finnigan MAT 95 XL, MS (ESI): Waters QTOF II and MS (CI): Waters Prospec Q. 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.

4.3. Electrophilic fluorination via trimethylsilyl enol ethers (route A)

The trimethylsilyl enol ethers, **4a–g**, were prepared as described by Wiles et al.[42] starting with 20 mmol of the acetophenones. Compound **4h** was prepared according to Schumacher and Reissig.[43] ^{1}H NMR spectra were in accordance with that reported previously: **4a**,[44] **4b**,[44] **4c**,[45] **4d**,[18] **4f**,[43] **4g**[46] and **4h**.[43] Compound **4e**: ^{1}H NMR ($CDCl_3$) δ: 0.26 (s, 9H), 4.44 (d, J=1.9 Hz, 1H), 4.89 (d, J=1.9 Hz, 1H) and 7.44 (m, 4H).

The crude trimethylsilyl enol ether **4** (20 mmol) dissolved in dry acetonitrile (50 mL) was added to a suspension of F–TEDA–BF_4 (20 mmol) in dry acetonitrile (150 mL). The reaction mixture was

stirred at room temperature and monitored by ^{1}H NMR spectroscopy until complete consumption of the trimethylsilyl enol ether. Additional F–TEDA–BF_4 (0.1–0.2 equiv) was added in cases where complete conversion was not obtained. A solvent switch from acetonitrile to EtOAc (100 mL) was performed. The organic phase was washed with water (2×100 mL) and brine (100 mL), and dried over Na_2SO_4 before the solvent was evaporated under reduced pressure. The crude products were purified as follows: **1a**, silica gel chromatography (pentane/EtOAc, 5:2); **1b**, crystallisation (*i*-PrOH); **1c**, bulb to bulb distillation (94–96 °C at 1.5×10^{-2} mbar); **1d**, silica gel chromatography (cyclohexane/acetone, 5:1); **1e**, silica gel chromatography (pentane/acetone, 10:1); **1f**, bulb to bulb distillation (83–85 °C at 7.5×10^{-2} mbar); **1g**, crystallisation (EtOH) and **1h**, silica gel chromatography ($CHCl_3$).

4.4. Electrophilic fluorination in methanol (route B)

The acetophenone (8.84 mmol) and F–TEDA–BF_4 (2 equiv) were mixed in methanol (64 mL) and stirred at reflux for 2–11 days. The reaction mixture was cooled to room temperature, and the methanol was removed under reduced pressure. The residue was diluted with dichloromethane (150 mL). The organic fraction was washed with water (2×30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was mixed with chloroform (15 mL), trifluoroacetic acid (3 mL) and water (3 mL). The acetals **6a**–**e** were cleaved at room temperature, whereas compounds **6f**–**h** were hydrolysed by refluxing for 20 h. Trifluoroacetic acid was neutralised by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with chloroform (3×25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Compounds were purified as follows **1a**: silica gel chromatography (pentane/EtOAc, 5:2), **1b**: crystallisation (*i*-PrOH), **1c**: silica gel chromatography (CH_2Cl_2), **1d**: silica gel chromatography (cyclohexane/acetone, 5:1), **1e**: silica gel chromatography (pentane/acetone, 10:1), **1f**: silica gel chromatography (CH_2Cl_2), **1g**: crystallisation (EtOH), **1h**: crystallisation (*i*-PrOH).

4.5. Nucleophilic displacement (route C)

Tetrabutylammonium hydrogen bifluoride (10 mmol in acetonitrile) was treated under a stream of nitrogen gas to remove acetonitrile prior to dilution with freshly distilled THF (25 mL). The α-bromoacetophenone (5 mmol) was dissolved in THF (25 mL) and added drop wise to the TBABF solution under a nitrogen atmosphere. The mixture was refluxed until TLC analysis indicated complete conversion. The reaction mixture was then diluted with diethyl ether (50 mL) and washed with dilute HCl (0.1 M, 3×20 mL) and water (2×30 mL). The water phase was back extracted twice with diethyl ether. The combined organic fractions were dried over $MgSO_4$, concentrated, and then subjected to purification by silica gel column chromatography (CH_2Cl_2/MeOH, 100:1).

4.6. Analytical data for α-fluoroacetophenones

*4.6.1. 2-Fluoro-1-(4-methoxyphenyl)ethanone (**1a**)*[47]

White solid, mp 79–80 °C (78–79 °C).[7] ^{1}H, ^{13}C and ^{19}F NMR were in accordance with that reported by Funabiki et al.[48] IR was in accordance with Barkakaty et al.[47] MS (EI, *m*/*z*, %): 168 (M^+, 6), 127 (8), 71 (6) and 43 (100). HRMS (EI): 168.0580 (calcd 168.0587).

*4.6.2. 1-(4-Benzyloxyphenyl)-2-fluoroethanone (**1b**)*

White solid, mp 110–111 °C. ^{1}H NMR ($CDCl_3$) δ: 5.14 (s, 2H), 5.46 (d, *J*=47.0 Hz, 2H), 7.02–4.04 (m, 2H), 7.36–7.43 (m, 5H) and 7.87–7.89 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 70.2, 83.5 (d, *J*=181.1 Hz), 115.0 (2C), 127.0, 127.5 (2C), 128.4, 128.8 (2C), 130.3 (d, *J*=2.9 Hz, 2C), 135.9, 163.4 and 191.9 (d, *J*=15.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −230.4 (t, *J*=47.0 Hz). IR (KBr, cm^{-1}): 2940, 1700, 1599, 1242, 1174, 1082, 1007, 975, 834 and 755. MS (EI, *m*/*z*, %): 244 (M^+, 3), 91 (100) and 65 (7). HRMS (EI): 244.0895 (calcd 244.0990).

*4.6.3. 2-Fluoro-1-phenylethanone (**1c**)*[14]

Clear oil, which solidified upon storage, mp 25–26 °C (26 °C).[49] NMR[14,50] and IR-spectra[21] were in accordance with that reported previously. MS (EI, *m*/*z*, %): 138 (M^+, 9), 105 (100) and 77 (64). HRMS (EI): 138.0483 (calcd 138.0481).

*4.6.4. 2-Fluoro-1-(4-fluorophenyl)ethanone (**1d**)*[19]

White solid, mp 49–51 °C (48–50 °C).[19] ^{1}H NMR ($CDCl_3$) δ: 5.49 (d, *J*=46.9 Hz, 2H), 7.15–7.21 (m, 2H) and 7.83–7.98 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 83.5 (d, *J*=186.7 Hz), 116.1 (d, *J*=22.0 Hz, 2C), 130.2 (dd, *J*=4.2 and 1.1 Hz), 130.7 (dd, *J*=12.1 and 3.1 Hz, 2C), 166.2 (d, *J*=255.0 Hz) and 192.0 (d, *J*=15.8 Hz). ^{19}F NMR ($CDCl_3$) δ: −103.3 (m) and −230.0 (t, *J*=47.0 Hz). IR (KBr, cm^{-1}): 2951, 1686, 1600, 1236, 1161, 1083, 976 and 835. MS (EI, *m*/*z*, %): 156 (M^+, 1), 123 (42), 95 (27) and 75 (10). HRMS (EI): 156.0379 (calcd 156.0387).

*4.6.5. 1-(4-Bromophenyl)-2-fluoroethanone (**1e**)*[25]

White solid, mp 72–73 °C (71–72 °C).[25] ^{1}H NMR was in agreement with Ying et al.[51] ^{13}C and ^{19}F NMR corresponded with that reported by Bridge et al.[25] IR was in accordance with Barkakaty et al.[47] MS (EI, *m*/*z*, %): 216/218 (M^+, 7), 183/185 (100), 155/157 (50) and 104 (40). HRMS (EI): 215.9585 (calcd 215.9586).

*4.6.6. 2-Fluoro-1-(4-trifluoromethylphenyl)ethanone (**1f**)*

White solid, mp 35–36 °C. ^{1}H NMR ($CDCl_3$) δ: 5.52 (d, *J*=46.8 Hz, 2H), 7.76–7.79 (m, 2H) and 8.02–8.04 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 83.8 (d, *J*=184.3 Hz), 123.4 (q, *J*=273 Hz), 126.0 (q, *J*=3.8 Hz, 2C), 128.6 (d, *J*=3.1 Hz, 2C), 135.4 (q, *J*=32.9 Hz), 136.5 (m) and 192.9 (d, *J*=16.4 Hz). ^{19}F NMR ($CDCl_3$) δ: −63.9 (s, 3F) and −230.2 (t, *J*=47.0 Hz). IR (KBr, cm^{-1}): 2937, 1707, 1418, 1330, 1175, 1066, 976 and 836. MS (EI, *m*/*z*, %): 206 (M^+, 0.1), 173 (35), 145 (100), 125 (29), 95 (17) and 75 (9). HRMS (EI): 206.0360 (calcd 206.0355).

*4.6.7. 1-(4-Cyanophenyl)-2-fluoroethanone (**1g**)*

White solid, mp 104–105 °C. ^{1}H NMR ($CDCl_3$) δ: 5.51 (d, *J*=46.8 Hz, 2H), 7.81 (m. 2H) and 8.02 (m, 2H). ^{13}C NMR ($CHCl_3$) δ: 83.8 (d, *J*=183.5 Hz), 117.4, 117.6, 128.6 (d, *J*=3.3 Hz, 2C), 132.7 (2C), 136.7 (d, *J*=1.1 Hz) and 192.7 (d, *J*=16.9 Hz). ^{19}F NMR ($CDCl_3$) δ: −229.6 (t, *J*=47.0 Hz). IR (KBr, cm^{-1}): 3095, 2932, 2231, 1709, 1437, 1232, 1083, 979 and 839. MS (EI, *m*/*z*, %): 163 (M^+, 2), 130 (100), 102 (56), 76 (11) and 75 (17). HRMS (EI): 163.0437 (calcd 163.0433).

*4.6.8. 2-Fluoro-1-(4-nitrophenyl)ethanone (**1h**)*[25]

Off-white solid, mp 96–97 °C (90–92 °C).[25] ^{1}H, ^{13}C and ^{19}F NMR corresponds with that of Bridge et al.,[25] except the C–F coupling constant for the carbonyl: 192.8 (d, *J*=17.0 Hz). IR (KBr, cm^{-1}): 3119, 2934, 1709, 1607, 1526, 1346, 1227, 1091, 973, 857 and 799. MS (EI, *m*/*z*, %): 183 (M^+, 1), 150 (100), 104 (33), 92 (15) and 76 (20). HRMS (EI): 183.0339 (calcd 183.0332).

4.7. Analytical data for impurities and intermediates

*4.7.1. 2-Fluoro-1-(3-fluoro-4-methoxyphenyl)ethanone (**5a**)*[7]

Synthesis according to route B. Compound **5a** was isolated by silica gel chromatography (pentane/EtOAc, 5:2) as a white solid mp 84–85 °C (82–84 °C).[7] ^{1}H NMR was in accordance with that reported previously.[7] ^{13}C NMR ($CDCl_3$) δ: 56.5, 83.8 (dd, *J*=182.9 and 0.7 Hz), 112.8 (d, *J*=2.0 Hz), 115.9 (dd, *J*=19.3 and 3.2 Hz), 125.7 (t, *J*=3.5 Hz), 127.1 (dd, *J*=5.3 and 1.2 Hz), 152.3 (dd, *J*=249.0 and 0.5 Hz), 153.0 (d, *J*=10.8 Hz) and 191.5 (dd, *J*=16.0 and 2.0 Hz). ^{19}F NMR ($CDCl_3$) δ: −133.3 (m) and −230.0 (t, *J*=46.9 Hz). IR (KBr, cm^{-1}): 2925, 2852, 1697, 1612, 1519, 1280, 1084, 1012 and 995. MS

(EI, *m*/*z*, %): 186 (M^+, 45), 153 (100), 125 (37), 110 (48), 95 (63) and 82 (47). HRMS (EI): 186.0497 (calcd 186.0492).

4.7.2. 1-(4-(Benzyloxy)-3-fluorophenyl)-2-fluoroethanone (**5b**)

Synthesis according to route B. The mother liquor after crystallisation of **1b** was concentrated, and compound **5b** was isolated by silica gel chromatography (CH_2Cl_2) yielding a white solid, mp 90–92 °C. ^{1}H NMR ($CDCl_3$) δ: 5.22 (s, 2H), 5.42 (d, J=47.0 Hz, 2H), 7.05 (m, 1H), 7.33–7.44 (m, 5H), 7.64 (m, 1H) and 7.68 (dd, J=11.5 and 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 71.4, 83.7 (dd, J=183.0 and 0.7 Hz), 114.6 (d, J=1.9 Hz), 116.2 (dd, J=19.5 and 3.2 Hz), 125.6 (t, J=3.4 Hz), 127.6 (2C), 128.7, 129.0 (2C), 130.5 (d, J=5.2 Hz), 135.6, 152.0 (d, J=10.8 Hz), 152.6 (dd, J=249.4 and 0.5 Hz) and 191.5 (dd, J=16.0 and 2.0 Hz). ^{19}F NMR ($CDCl_3$) δ: −132.7 (m) and −230.0 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2933, 1707, 1687, 1608, 1517, 1275, 1081 and 994. MS (EI, *m*/*z*, %): 262 (M^+, 2), 139 (7), 91 (100) and 65 (8). HRMS (EI): 262.0804 (calcd 262.0805).

4.7.3. 1-(2-Fluoro-1,1-dimethoxyethyl)-4-methoxybenzene (**6a**)

Compound **6a** was synthesised from **1a** according to Ranu et al.[30] Compound hydrolysed during work-up yielding only 4 mg (5%) after silica gel chromatography (hexane/EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ: 3.27 (s, 6H), 3.82 (s, 3H), 4.48 (d, J=47.2 Hz, 2H), 6.91 (m, 2H) and 7.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 49.1 (2C), 55.3, 83.5 (d, J=178.1 Hz), 100.4 (d, J=20.1 Hz), 113.6 (2C), 128.5 (d, J=0.9 Hz, 2C), 130.2 (d, J=0.9 Hz) and 159.7. ^{19}F NMR ($CDCl_3$) δ: −228.7 (t, J=47.4 Hz). IR (KBr, cm^{-1}): 2942, 2837, 1612, 1513, 1250, 1071 and 1038. MS (EI, *m*/*z*, %): 214 (M^+, 6), 183 (62), 181 (100), 149 (40), 135 (88), 121 (25) and 107 (41). HRMS (EI): 214.1000 (calcd 214.1005).

4.7.4. 1-(Benzyloxy)-4-(2-fluoro-1,1-dimethoxyethyl)benzene (**6b**)

Compound **6b** was purified by silica gel chromatography (pentane/EtOAc, 9:1) yielding a white sold, mp 64.5–66.5 °C. ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 6H), 4.51 (d, J=47.3 Hz, 2H), 5.10 (s, 2H), 7.02 (m, 2H), 7.36 (m, 2H) and 7.40–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 49.3 (2C), 70.2, 83.7 (d, J=178.2 Hz), 100.6 (d, J=20.0 Hz), 114.6 (2C), 127.7 (2C), 128.2, 128.8 (2C), 128.8 (2C), 130.6, 137.1 and 159.1. ^{19}F NMR ($CDCl_3$) δ: −228.7 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2935, 2830, 1610, 1514, 1454, 1247, 1098 and 1038. MS (EI, *m*/*z*, %): 291 (M^++1, 4), 260 (24), 259 (50), 258 (73), 169 (5), 167 (5), 92 (34), 91 (100) and 65 (26). HRMS (EI): 290.1305 (calcd 290.1318).

4.7.5. 1-Bromo-4-(2-fluoro-1,1-dimethoxyethyl)benzene (**6e**)

The dimethyl acetal **6e** was purified by silica gel chromatography (CH_2Cl_2) yielding a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 3.27 (s, 6H), 4.47 (d, J=47.1 Hz, 2H), 7.40 (m, 2H) and 7.52 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 49.3 (2C), 83.2 (d, J=178.2 Hz), 100.4 (d, J=20.4 Hz), 123.0, 129.3 (d, J=0.9 Hz, 2C), 131.6 (2C) and 137.5 (d, J=0.5 Hz). ^{19}F NMR ($CDCl_3$) δ: −229.8 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2944, 2836, 1592, 1485, 1394, 1290, 1071, 826 and 743. MS (EI, *m*/*z*, %): 264 (35), 262 (36), 245 (36), 243 (32), 234 (64), 233 (86), 232 (82), 231 (100), 230 (78), 229 (93), 216 (31), 201 (7), 199 (9), 105 (10) and 91 (17). HRMS (EI): 262.0006 (calcd 262.0005).

4.7.6. 1-(2-Fluoro-1,1-dimethoxyethyl)-4-(trifluoromethyl)-benzene (**6f**)

The dimethyl acetal **6f** was purified by silica gel chromatography (pentane/acetone, 7:1) yielding a clear oil. ^{1}H NMR ($CDCl_3$) δ: 3.30 (s, 6H), 4.51 (d, J=47.0 Hz, 2H) and 7.66 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 49.2 (2C), 82.9 (d, J=178.2 Hz), 100.2 (d, J=20.6 Hz), 124.1 (q, J=272.3 Hz), 125.2 (q, J=3.8 Hz, 2C), 127.8 (d, J=0.9 Hz, 2C), 130.7 (q, J=32.4 Hz) and 142.3 (m). ^{19}F NMR ($CDCl_3$) δ: −63.2 (s) and −230.3 (t, J=47.0 Hz). IR (KBr, cm^{-1}): 2949, 2839, 1620, 1411, 1327, 1166 and 845. MS (EI, *m*/*z*, %): M^+—missing, 221 (32), 219 (100), 173 (47), 159 (17), 145 (31) and 109 (24). HRMS (EI): not obtained, molecular ion unstable.

4.7.7. 4-(2-Fluoro-1,1-dimethoxyethyl)benzonitrile (**6g**)

The dimethyl acetal **6g** was purified by silica gel chromatography ($CHCl_3$) yielding colourless oil. ^{1}H NMR ($CDCl_3$): 3.27 (s, 6H), 4.48 (d, J=47.0 Hz, 2H) and 7.67 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 49.4 (2C), 82.6 (d, J=178.2 Hz), 100.2 (d, J=19.8 Hz), 112.6, 118.8, 128.4 (d, J=1.0 Hz, 2C), 132.2 (2C) and 143.7. ^{19}F NMR ($CDCl_3$) δ: −230.7 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2943, 2843, 2232, 1610, 1294, 1067 and 1034. MS (EI, *m*/*z*, %): 209 (M^+, 6), 179 (43), 178 (95), 177 (76), 176 (100), 146 (8), 130 (64) and 104 (5). HRMS (EI): 209.0855 (calcd 209.0852).

4.7.8. 1-(Fluoro-1,1-dimethoxyethyl)-4-nitrobenzene (**6h**)

The dimethyl acetal **6h** was purified by silica gel chromatography ($CHCl_3$), yielding a with solid, mp 45–46 °C. ^{1}H NMR ($CDCl_3$) δ: 3.29 (s, 6H), 4.50 (d, J=47.0 Hz, 2H), 7.72 (m, 2H) and 8.24 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 49.4, 82.6 (d, J=178.1 Hz), 100.2 (d, J=20.8 Hz), 123.5 (2C), 128.7 (2C), 145.6 (d, J=3.5 Hz) and 148.2. ^{19}F NMR ($CDCl_3$) δ: −230.8 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 3001, 2941, 1609, 1522, 1354, 1288, 1090 and 1071. MS (CI, CH_4–Cl, *m*/*z*, %): 231 (M^++2, 11) and 230 (M^++1, 100). HRMS (CI, CH_4–Cl): 230.0821 (calcd for $C_{10}H_{13}FNO_4^+$ 230.0823).

4.7.9. 1-(Benzyloxy)-2-fluoro-4-(2-fluoro-1,1-dimethoxyethyl)benzene (**7b**)

Compound **7b** was isolated by silica gel chromatography (pentane/EtOAc, 9:1) yielding a yellowish oil. ^{1}H NMR ($CDCl_3$) δ: 3.29 (s, 6H), 4.47 (d, J=47.4 Hz, 2H), 5.16 (s, 2H), 7.20 (m, 1H), 7.29 (dd, J=12.5 and 2.0 Hz, 1H) and 7.32–7.49 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 49.4 (2C), 71.5, 83.3 (d, J=178.2 Hz), 100.1 (dd, J=20.8 and 1.7 Hz), 115.2 (d, J=2.0 Hz), 115.8 (d, J=20.4 Hz), 123.3 (d, J=2.9 Hz), 127.6 (2C), 128.4, 128.9 (2C), 132.0 (d, J=5.4 Hz), 136.7, 147.0 (d, J=10.8 Hz) and 152.8 (d, J=245.9 Hz). ^{19}F NMR ($CDCl_3$) δ: −134.3 (m) and −229.3 (t, J=46.9 Hz). IR (KBr, cm^{-1}): 2943, 2836, 1601, 1515, 1276, 1072 and 1036. MS (EI, *m*/*z*, %): 308 (M^+, 31), 277 (58), 276 (53), 275 (88), 257 (53), 186 (27), 183 (18) and 91 (100). HRMS (EI): 308.1218 (calcd 308.1224).

4.7.10. trans-1,2,3-Tribenzoylcyclopropane (**8c**)[35]

Compound **8c** was isolated after synthesis according to route C by silica gel chromatography (CH_2Cl_2/MeOH, 100:1) and re-crystallised from EtOAc yielding a white solid, mp 216–217 °C (216–217 °C).[52] ^{1}H NMR corresponds with that of Fuhrmann et al.[36] ^{13}C NMR ($CDCl_3$) δ: 30.4, 36.4 (2C), 128.5 (4C), 128.7 (4C), 128.8 (2C), 128.9 (2C), 133.6 (2C), 134.0, 136.5 (3C), 193.0 (2C) and 196.0. IR (KBr, cm^{-1}): 3066, 3042, 2999, 1685, 1672, 1596, 1447, 1330, 1220 and 715. MS (EI, *m*/*z*, %): 354 (M^+, 1), 249 (32), 233 (9), 105 (100) and 77 (38). HRMS (EI): 354.1262 (calcd 354.1256).

4.7.11. trans-1,2,3-Tri(4-fluorobenzoyl)cyclopropane (**8d**)

trans-1,2,3-Tri(4-fluorobenzoyl)cyclopropane (**8d**) was isolated after synthesis according to route C by silica gel chromatography (CH_2Cl_2). White solid, mp 200–202 °C. ^{1}H NMR ($CDCl_3$) δ: 3.69 (d, J=5.6 Hz, 2H), 4.15 (t, J=5.6 Hz, 1H), 7.09–7.13 (m, 4H), 7.18–7.22 (m, 2H), 8.01–8.03 (m, 4H) and 8.21–8.24 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 30.3, 36.0 (2C), 116.0 (d, J=22.0 Hz, 4C), 116.1 (d, J=22 Hz, 2C), 131.4 (d, J=9.5 Hz, 4C), 131.5 (d, J=9.6 Hz, 2C), 132.8 (d, J=2.7 Hz, 2C), 132.8 (d, J=2.7 Hz), 166.1 (d, J=256.1 Hz, 2C), 166.4 (d, J=256.8 Hz), 191.3 (2C) and 194.1. IR (KBr, cm^{-1}): 3068, 3018, 1684, 1665, 1597, 1506, 1227, 1156 and 849. MS (EI, *m*/*z*, %): 408 (M^+, 7), 409 (2), 286 (55), 285 (92), 269 (57), 124 (65), 123 (100) and 95 (90). HRMS (EI): 408.0977 (calcd 408.0973).

4.7.12. trans-1,2,3-Tri(4-bromobenzoyl)cyclopropane (**8e**)[53]

trans-1,2,3-Tri(4-bromobenzoyl)cyclopropane (**8e**) was isolated after synthesis according to route C by silica gel chromatography (CH_2Cl_2/MeOH, 100:1). White solid, mp 198–200 °C. ^{1}H NMR ($CDCl_3$) δ: 3.69 (d, J=5.6 Hz, 2H), 4.13 (t, J=5.6 Hz, 1H), 7.59–7.61 (m, 4H), 7.67–7.70 (m, 2H), 7.85–7.87 (m, 4H) and 8.03–8.06 (m, 2H). ^{13}C NMR

($CDCl_3$) δ: 30.3, 36.1 (2C), 129.1 (2C), 129.6, 129.9 (4C), 130.2 (2C), 132.1 (4C), 132.3 (2C), 135.0 (3C), 191.8 (2C) and 194.6. IR (KBr, cm^{-1}): 3052, 1693, 1670, 1397, 1317, 1296, 1204, 1072 and 1008. MS (EI, *m*/*z*, %): 589/591 (M^+, 1), 406 (17), 185 (59), 183 (58), 157 (14), 155 (14) and 28 (100). HRMS (EI): 589.8529 (calcd for $C_{24}H_{15}O_3^{79}Br^{81}Br_2$: 589.8551).

*4.7.13. (3-(Bromomethyl)-3-(4-fluorophenyl)oxiran-2-yl)(4-fluorophenyl)methanone (**9d**)*

Compound **9d** was isolated after synthesis according to route C by column chromatography (CH_2Cl_2) starting with **3d**. ^1H NMR ($CDCl_3$) δ: 3.67 (d, *J*=11.1 Hz, 1H), 3.80 (d, *J*=11.1 Hz, 1H), 4.38 (s, 1H), 7.11–7.23 (m, 4H), 7.55–7.60 (m, 2H) and 8.04–8.09 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 31.4, 64.8, 116.0 (d, *J*=21.8 Hz, 2C), 116.4 (d, *J*=22.1 Hz, 2C), 128.3 (d, *J*=8.4 Hz, 2C), 131.4 (d, *J*=9.6 Hz, 2C), 132.2 (d, *J*=3.1 Hz), 132.4 (d, *J*=3.3 Hz), 163.1 (d, *J*=248.8 Hz), 166.5 (d, *J*=257.3 Hz) and 190.2.

*4.7.14. 1-(2-(4-(Benzyloxy)phenyl)-2-oxoethyl)pyridinium bromide (**10b**)*

1-(2-(4-(Benzyloxy)phenyl)-2-oxoethyl)pyridinium bromide precipitated from the reaction mixture upon fluorination of **3b** using TBABF in the presence of pyridine. It was also synthesised from **3b**. 1-(4-Benzyloxyphenyl)-2-bromoethanone (**3b**) (1.5 g, 4.9 mmol) dissolved in THF (25 mL) was treated with pyridine (0.93 g, 12 mmol) and stirred at 45 °C for 5 h. THF was removed and the residue was re-crystallised from ethanol utilising diethyl ether as anti solvent, yielding 1.2 g (64%) of a slight yellowish solid, mp 198–200 °C. ^1H NMR (DMSO) δ: 5.29 (s, 2H), 6.44 (s, 2H), 7.26–7.28 (m, 2H), 7.36–7.50 (m, 5H), 8.03–8.05 (m, 2H), 8.27 (t, 2H), 8.73 (t, 1H) and 8.99 (d, 2H). ^{13}C NMR ($CDCl_3$) δ: 66.5, 70.3, 115.9 (2C), 127.1 (2C), 128.4 (2C), 128.7, 129.1 (2C), 131.3 (2C), 136.8, 146.9 (2C), 163.9 and 189.5. IR (KBr, cm^{-1}): 3028, 2939, 1690, 1670, 1636, 1599, 1492, 1240, 1173, 990, 834, 752 and 686. HRMS (ESI): 304.1331 (calcd for $C_{20}H_{18}NO_2^+$: 304.1332).

*4.7.15. 1-(2-Oxo-2-phenylethyl)pyridinium bromide (**10c**)*[54]

Compound **10c** was isolated as described for **10b**. ^1H and ^{13}C NMR were in accordance with Szwajca et al.[54]

*4.7.16. 2-(4-(Benzyloxy)phenyl)-N,N,N-triethyl-2-oxoethanaminium bromide (**11b**)*

The identity of **11b** was confirmed by synthesis of a reference sample. 1-(4-Benzyloxyphenyl)-2-bromoethanone (**3b**) (1.5 g, 4.9 mmol) in THF (25 mL) was mixed with triethylamine (1.0 g, 10 mmol) and heated at 50 °C. After 5 h the reaction mixture was cooled to room temperature and diethyl ether (25 mL) was added. The solid material obtained after filtration was re-crystallised from isopropanol, yielding 1.51 g (75%) of a white solid, mp 162–164 °C. ^1H NMR ($CDCl_3$) δ: 1.41 (t, *J*=7.3 Hz, 9H), 3.87 (q, *J*=7.3 Hz, 6H), 5.13 (s, 2H), 5.45 (s, 2H), 7.05–7.07 (m, 2H), 7.35–7.40 (m, 5H) and 8.34–8.36 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 8.4 (3C), 54.6 (3C), 59.9, 70.2, 115.2 (2C), 126.7, 127.4 (2C), 128.2, 128.6 (2C), 131.6 (2C), 135.7, 164.2 and 189.5. IR (KBr, cm^{-1}): 2974, 2913, 1687, 1601, 1576, 1456, 1237, 1006, 833 and 755. HRMS (ESI): 326.2116 (calcd for $C_{21}H_{28}NO_2^+$ 326.2115).

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