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A general method of halogenation for synthesis of α-halodifluoromethyl ketones and [^{18}F]-labeled trifluoromethyl ketones

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Abstract

A convenient general method of halogenations suitable for synthesis of α-halodifluoromethyl ketones is reported. Reaction of 2,2-difluoro-1-aryl-1-trimethylsiloxyethenes (difluoro silyl enol ethers) (**2a–e**) with halogens at low temperature (−30 to −78 °C) produced a high yield of α-halodifluoromethyl ketones (**1a–j**). This one-step simple method can be highly useful for synthesis of [^{18}F]-labeled α-trifluoromethyl ketones.

Keywords: Halogenation; Electrophilic fluorination; Fluorine-18

1. Introduction

α-Trifluoromethyl ketones (TFMKs) are biologically active compounds of increasing interest [1]. Many of these compounds have been found to be potential hydrolytic enzyme inhibitors, such as protease inhibitors. Due to their unique property of forming stable tetrahedral hemiacetals or hydrates, they act as transition-state analogues of substrates for enzymes [1–5] TFMKs have also been demonstrated as cytotoxic agents against human oral tumor cell lines, such as human squamous carcinoma cells HSC-2 and salivary gland tumor cells HSG [6]. α-TFMKs have potential for radiolabeling with ^{18}F, where they can be used as markers for cell proliferation or viral infection.

Many [^{18}F]-labeled compounds are used for in vivo non-invasive imaging of tumor and gene expression by positron emission tomography (PET), and thus are very useful for diagnosis of disease and detecting metabolic parameters, especially in the field of oncology [7]. Several types of ^{18}F-labeled PET imaging agents have been developed, including ^{18}F-labeled sugars [8,9], steroids [7] proteins and peptides [10,11]. Some of us have developed [^{18}F]-labeled nucleoside analogues 2′-deoxy-2′-fluoro-5-methyl-1-β-D-arabinofuranosyluracil ([^{18}F]-FMAU) [12], 9-[(3-[^{18}F]-fluoro-1-hydroxy-2-propoxy) methyl]guanine ([^{18}F]-FHPG) [13] and 9-[(4-[^{18}F]-fluoro-3-hydroxymethyl-butyl]guanine ([^{18}F]-FHBG) [14] as potential PET agents for cancer diagnosis gene expression.

TFMKs are traditionally prepared from inexpensive trifluoroacetic acid derivatives [15,16]. Recently, we reported the direct preparation of TFMKs from carboxylic esters with (trifluoromethyl)trimethylsilane (TMS-CF_3) [17]. This method has been further extended by others with CsF catalyzed trifluoromethylation of esters [18]. However, these methods are not suitable for synthesis of [^{18}F]-labeled TFMKs since it is difficult to prepare [^{18}F]-labeled trifluoroacetic acid derivatives or TMS-CF_3 due to the short half-life of ^{18}F ($t_{1/2}$ = 110 min).

Herein, we report the first convenient method of fluorination using 2,2-difluoro-1-aryl-1-trimethylsiloxyethenes (2,2-difluoro silyl enol ethers) with elemental fluorine (F_2). This method is suitable for radiochemical synthesis of [^{18}F]-labeled TFMKs. The methodology has been extended to synthesize other halodifluoromethyl ketones by reacting 2,2-difluoro silyl enol ethers with respective halogens, such as Br_2 and I_2. The halogenodifluoromethyl ketones may have potential biological activities.

2. Experimental

2.1. Reagents and instrumentation

All reagents and solvents were purchased from Aldrich (Milwaukee, WI), and used without further purification,

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unless otherwise specified. Dichloromethane (CH_2Cl_2) and fluorotrichloromethane ($CFCl_3$) were distilled over calcium hydride (CaH_2), and acetonitrile (CH_3CN) was distilled over phosphorus pentoxide (P_2O_5) prior to use. Column chromatography was performed using silica gel (60–200 meshes). Thin layer chromatography (TLC) was performed on silica gel plate (1 cm × 10 cm) and developed in the appropriate solvent system (hexane:ethyl acetate, 9:1).

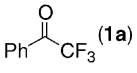
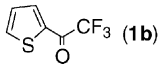
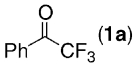
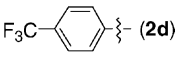
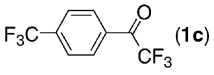
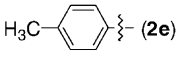
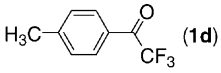
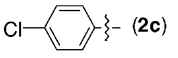
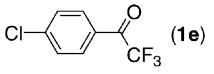
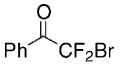
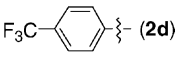
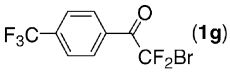
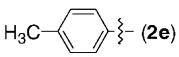
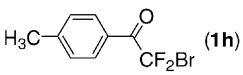
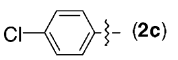
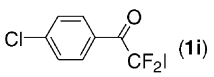
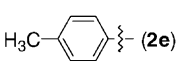
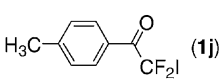
Proton, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AMX-500 or WP-360 NMR spectrometer in chloroform-D using tetramethysilane and trichlorofluoromethane as internal reference, respectively. Mass spectra were obtained on a Hewlett-Packard 5890 gas chromatograph equipped with a Hewlett-Packard 5971 mass selective detector.

2.2. Preparation of 2,2-difluoro-1-aryl-1-trimethylsiloxyethenes (2a–e)

2,2-Difluoro silyl enol ethers (**2a–e**) were prepared via magnesium metal mediated reductive defluorination of TFMKs. All 2,2-difluoro silyl enol ethers were prepared following a similar procedure. A representative method is described below. To a dry 250 ml Schlenk flask was added magnesium turnings (1.45 g, 60 mmol), dry tetrahydrofuran (THF, 120 ml) and chlorotrimethylsilane (TMSCl, 13.0 g, 120 mmol), and the flask was cooled down to 0 °C. 2,2,2-Trifluoroacetophenone (**1a**, 5.2 g, 30 mmol) was added dropwise into the flask via a syringe. After addition, the reaction mixture was stirred for additional 1 h. The completion of the reaction was monitored by ^{19}F NMR. The solvent and excess TMSCl were removed under vacuum, and hexane (50 ml) was added to the residue. Solid impurities were filtered off by suction filtration, and the solvent was evaporated to afford 2,2-difluoro-1-phenyl-1-trimethylsiloxyethene (**2a**, 6.8 g, 99% yield). ^1H NMR: $\delta = 0.60$ (s, 9H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 2H), 7.61 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR: $\delta = 0.02$, 114.09 (q, $^2J_{C-F} = 18.0$ Hz), 125.84, 127.72, 128.25, 132.71, 154.87 (t, $^1J_{C-F} = 286.8$ Hz); ^{19}F NMR: $\delta = -100.39$ (d, $^2J_{F-F} = 68.0$ Hz), −112.16 (d, $^2J_{F-F} = 68.0$ Hz). MS (70 eV, *m/z*): 228 (M^+), 213, 197, 186, 177, 131, 115, 105, 89, 81, 77, 73.

Other 2,2-difluoro silyl enol ethers (**2b–e**, entries 2–5 in Table 1) were also characterized by spectroscopic methods and found to be consistent with the previous report [19–23].

Table 1
Preparation of halogenated methyl ketones **1** through facile selective halogenations of 2,2-difluoro silyl enol ethers **2**

Entry	Substrate **2**	Halogenating agent	Product **1**	Yield (%)[a]
1	R = Ph (**2a**)	F_2	 (**1a**)	69
2	 (**2b**)	F_2	 (**1b**)	78[b]
3	Ph (**2a**)	Selectfluor™	 (**1a**)	89
4	 (**2d**)	Selectfluor™	 (**1c**)	88
5	 (**2e**)	Selectfluor™	 (**1d**)	87
6	 (**2c**)	Selectfluor™	 (**1e**)	90
7	Ph (**2a**)	Br_2	 (**1f**)	85
8	 (**2d**)	Br_2	 (**1g**)	87
9	 (**2e**)	Br_2	 (**1h**)	88
10	 (**2c**)	I_2	 (**1i**)	60
11	 (**2e**)	I_2	 (**1j**)	39

[a] Isolated yield.
[b] Determined by ^{19}F NMR.

2.3. Fluorinations of 2,2-difluoro-1-aryl-1-trimethylsiloxyl-ethene (**2a–e**)

All experiments were performed under a similar condition. A representative method is described. Compound **2a** (200 mg, 0.88 mmol) was dissolved in dry acetonitrile (20 ml) and cooled to −45 °C. A mixture of fluorine and nitrogen ($F_2/N_2 = 1/4$ (v/v)) was bubbled for 15 min (in excess). The reaction mixture was warmed to room temperature, and 5 ml of ice water was added. The mixture was extracted with ether (2 × 10 ml), and the ether phase was dried over $MgSO_4$ and filtered. After removal of the solvent, crude trifluoroacetophenone was obtained in 83% yield. The crude product was purified by flash chromatography on a silica gel column using 10% ethyl acetate in hexane as eluent to give 106 mg 2,2,2-trifluoroacetophenone (**1a**) as colorless liquid in 69% yield. ^{1}H NMR: $\delta = 7.56$ (t, $J = 7.8$ Hz, 2H); 7.72 (t, 1H, $J = 7.3$ Hz); 8.08 (d, $J = 8.1$ Hz, 2H). ^{13}C NMR: $\delta = 116.67$ (q, $^1J_{C-F} = 291.7$ Hz); 129.06; 129.90; 130.06; 135.49; 181.05 (t, $^2J_{C-F} = 35.2$ Hz). ^{19}F NMR: $\delta = -71.85$. MS (70 eV, *m/z*): 174 (M^+); 123 ($M^+ - 51$); 105 ($PhCO^+$); 77; 69; 51.

The typical fluorination procedure with Selectfluor™ is as follows. Compound **2a** was added into a acetonitrile solution (20 ml) of Selectfluor™ (1.0 g, 2.8 mmol) at −78 °C (0.51 g, 2.2 mmol) in 5 ml of dichloromethane. Then the reaction mixture was allowed to warm up to 0 °C slowly over a period of 2 h. The reaction mixture was quenched by adding 15 ml of ice water and 20 ml of dichloromethane. The organic phase was separated and dried over magnesium sulfate. After removal of the solvent and flash chromatography on silica gel using ethyl acetate:hexanes (1:1) as eluent afforded 0.34 g of compound (**1a**) in 89% yield.

All other trifluoromethyl ketones (**1b–e**, entries 2–5 in Table 1) prepared either by fluorine or Selectfluor™ were characterized and found to be consistent with the reported data [15].

2.4. Brominations of 2,2-difluoro-1-aryl-1-trimethylsiloxyl-ethene (**2a,d,e**)

All bromination reactions were performed in the similar way and a representative procedure is described. Compound **2a** (6.08 g, 26.7 mmol) was dissolved in 50 ml dry CH_2Cl_2, and cooled to −78 °C. Liquid bromine was added via a syringe until the color of bromine no longer persisted. After stirring for another 30 min, the solvent in the reaction mixture was evaporated under vacuum, and the residue was extracted with CH_2Cl_2. The organic phase was further washed with $NaHCO_3$, brine and water subsequently. After drying over $MgSO_4$ and solvent removal, the crude product was purified by column chromatography using silica gel and hexanes as eluent to afford 5.33 g of 2-bromo-2,2-difluoroacetophenone (**1f**) in 85% yield. ^{1}H NMR: $\delta = 7.53$ (t, $J = 7.8$ Hz, 2H); 7.68 (t, $J = 7.8$ Hz, 1H); 8.15 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR: $\delta = 113.56$ (t, $^1J_{C-F} = 319.1$ Hz); 128.87; 129.05; 130.61 (t, $^3J_{C-F} = 2.6$ Hz); 135.09; 181.32 (t, $^2J_{C-F} = 26.0$ Hz). ^{19}F NMR: $\delta = -58.29$. MS (70 eV, *m/z*): 234 (M^+); 105 ($PhCO^+$); 77 (Ph^+).

2-Bromo-2,2-difluoro-4′-trifluoromethyl-acetophenone (**1g**): ^{1}H NMR: $\delta = 7.80$ (d, $J = 8.7$ Hz, 2H); 8.26 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR: $\delta = 113.18$ (t, $^1J_{C-F} = 318.2$ Hz); 123.22 (q, $^1J_{C-F} = 273.2$ Hz); 125.95 (q, $J = 4.2$ Hz); 131.01 (t, $J = 2.8$ Hz); 131.96; 136.21 (q, $J = 33.3$ Hz); 180.54 (t, $J = 27.7$ Hz). ^{19}F NMR: $\delta = -59.22$ (s, 2F); −63.96 (s, 3F). MS (70 eV, *m/z*): 304 (M^+); 223 ($CF_3C_6H_4COCF_2^+$); 119 ($CF_3C_6H_4CO^+$); 91; 65.

2-Bromo-2,2-difluoro-4′-methyl-acetophenone (**1h**): ^{1}H NMR: $\delta = 2.39$ (s, 3H); 7.25 (d, $J = 8.5$ Hz, 2H); 7.98 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR: $\delta = 21.70$; 113.64 (t, $^1J_{C-F} = 318.4$ Hz); 129.55; 130.65; 131.07; 146.54; 180.90 (t, $^2J_{C-F} = 26.5$ Hz). ^{19}F NMR: $\delta = -57.98$. MS (70 eV, *m/z*): 248 (M^+); 131; 119 ($CH_3C_6H_4CO^+$); 91; 81; 65; 51.

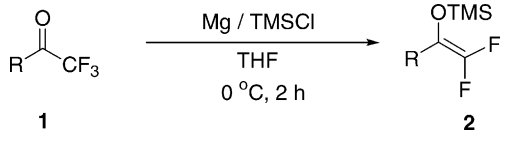
2.5. Iodinations of 2,2-difluoro-1-aryl-1-trimethylsiloxyl-ethene (**2c,e**)

The iodination reactions were carried out with iodine in dichloromethane as follows. Into a 10 ml of dichloromethane solution of 2,2-difluoro-1-(4′-chloro-phenyl)-1-trimethylsiloxyethene (**2c**, 200 mg, 0.76 mmol) at −78 °C, was added 0.19 g iodine (0.75 mmol). After warming up to room temperature, the reaction mixture was stirred overnight. Then 10 ml of sodium sulfite (10% aqueous solution) was added to remove excess iodine, followed by washing with 5 ml of brine. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed by rotary evaporator. The crude product was purified by flash chromatography a silica gel column and eluted with pentane to give 137 mg of the product 2-iodo-2,2-difluoro-4′-chloroacetophenone (**1i**) as a white solid in 60% yield. ^{1}H NMR: $\delta = 7.51$ (d, $J = 8.9$ Hz, 2H); 8.11 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR: $\delta = 95.13$ (t, $^1J_{C-F} = 326.4$ Hz); 126.67; 129.37; 132.18 (t, $^3J_{C-F} = 3.4$ Hz); 1412.85; 181.29 (t, $^2J_{C-F} = 23.6$ Hz). ^{19}F NMR: $\delta = -55.16$. MS (70 eV, *m/z*): 316 (M^+); 177; 158; 139 ($ClC_6H_4CO^+$); 127; 111; 75.

2-Iodo-2,2-difluoro-4′-methyl-acetophenone (**1j**): ^{1}H NMR: $\delta = 2.46$ (s, 3H); 7.32 (d, $J = 8.3$ Hz, 2H); 8.07 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR: $\delta = 21.89$; 95.79 (t, $^1J_{C-F} = 325.5$ Hz); 125.78; 129.63; 130.98 (t, $J = 2.5$ Hz); 146.43; 182.04 (t, $^2J_{C-F} = 22.9$ Hz). ^{19}F NMR: $\delta = -54.41$. MS (70 eV, *m/z*): 296 (M^+); 177; 127; 119 ($CH_3C_6H_4CO^+$); 91; 65.

3. Results and discussion

Preparation of 2,2-difluoro silyl enol ethers (**2a–e**) is represented in Scheme 1. Compounds **2a–e** were prepared

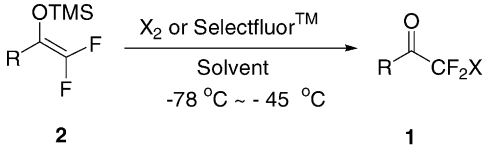


Scheme 1.

via magnesium metal mediated reductive defluorination of TFMKs **1a–e**, which was first developed by Uneyama's group [19] and later was applied by us in the preparation of di- and monofluoromethyl ketones (Scheme 1) [20]. The reaction was extremely facile under mild conditions and gave excellent yield of products **2a–e** (>85%). After removal of the insoluble material (solid Mg and $MgCl_2$) by filtration and evaporation of the solvent fairly pure product was obtained. These materials could be used for the next step for halogenations without further purification. ^{1}H and ^{19}F NMR spectra showed no significant impurities, with results consistent with the literature [19,20]. These silyl enol ethers **2a–e** are much more stable towards hydrolysis than normal silyl enol ethers, which enables the simple handling of these compounds for the subsequent studies.

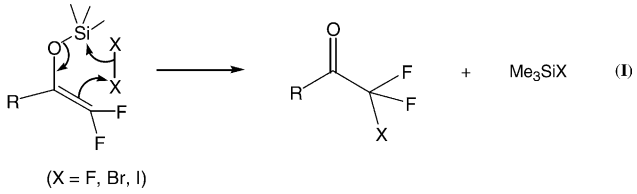
Scheme 2 represents the halogenation reactions of 2,2-difluoro silyl enol ethers. Compounds **1a–j** were prepared by reaction of the respective 2,2-difluoro silyl enol ethers (**2a–e**) with appropriate halogens as represented in Table 1. For fluorination two different reagents were used to compare the yields. Reactions were performed either in acetonitrile or fluorotrichloromethane (Freon-11) as solvent at low temperatures (Scheme 2). Experiments with F_2 were performed in CH_3CN by bubbling the F_2 gas as a mixture of normal fluorine [^{19}F]-F_2, 20 vol.% in nitrogen. The bromination and iodination procedures were similar to fluorinations, with some minor differences. Both reactions were carried out in dichloromethane between −78 °C and room temperature.

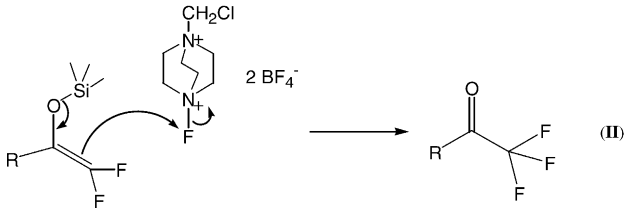
The fluorination reactions with F_2 produced good yields of the corresponding TFMKs (entries 1–2 in Table 1), which were consistent with the fluorination of non-fluorinated silyl enol ethers as reported by Purrington et al. [24]. When Selectfluor® [F-TEDA-BF4, *N*-fluoro-*N*-chloromethyl-triethylenediamine bis-(tetra-fluoroborate)] was applied as the electrophilic fluorination reagent, the reaction proceeded also quite efficiently in acetonitrile and gave excellent yield of TFMKs (entries 3–6 in Table 1). The bromination reactions were facile in dichloromethane even at, −78 °C to produce bromodifluoromethyl ketones in excellent yields



(X = F, Br, I; Solvent = CH_3CN, $CFCl_3$, CH_2Cl_2)

Scheme 2.





Scheme 3.

(entries 7–9 in Table 1). The slow addition of bromine into the dichloromethane solution is similar to a colorimetric titration process, in which the completion of the reaction could be monitored by the persistence of the bromine color. However, iodinations produced relatively lower yields compared to other halogens due to the lower electrophilicity of iodine. The iodination reactions need longer reaction times and gave moderate yields of iododifluoromethyl ketones (entries 10–11 in Table 1).

The mechanism of these selective halogenation reactions is shown in Scheme 3. The reaction with elemental halogens, such as F_2, Br_2 and I_2 is proposed to proceed via a six-membered transition state (Eq. (1)), whereas that with Selectfluor™ proceeds through an electrophilic substitution.

The fluorination method using F_2 has a great potential in synthesis of [^{18}F]-labeled α-trifluoromethyl ketones. Reaction of these 2,2-difluoro silyl ethers with cyclotron generated [^{18}F]-F_2 will produce [^{18}F]-labeled TFMKs. The bromo- and iododifluoromethyl ketones may be potentially useful in biological studies and/or intermediates for α-substituted-difluoromethyl ketones.

4. Conclusion

A general method of halogenations suitable for synthesis of α-halo-difluoromethyl ketones has been developed. This method is very simple and convenient, which produced good to excellent yield of the halogenated products. Model reactions with F_2 are highly useful for synthesis of [^{18}F]-labeled α-trifluoromethyl ketones for PET iamging.

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