

Research Article

Expedient synthesis of [^{18}F]-labeled α -trifluoromethyl ketones

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Summary

Several [^{18}F]-labeled α -trifluoromethyl ketones have been synthesized. Reactions of 2,2-difluoro-1-aryl-1-trimethylsiloxyethenes (**1a–d**) with [^{18}F]- F_2 at low temperature produced [^{18}F]-labeled α -trifluoromethyl ketones (**2a–d**). Radio-labeled products were isolated by purification with column chromatography in 22–28% yields, decay corrected (d.c.) in three runs per compound. Radiochemical purity was > 99% with specific activities 15–20 GBq/mmol at the end of synthesis (EOS). The synthesis time was 35–40 min from the end of bombardment (EOB). This one-step simple method is highly useful for the radiochemical synthesis of potential biologically active [^{18}F]-labeled α -trifluoromethyl ketones for PET imaging. Copyright © 2003 John Wiley & Sons, Ltd.

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Introduction

α -Trifluoromethyl ketones (TFMKs) are biologically active compounds of increasing interest.¹ Many of these compounds have been found to be

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potential hydrolytic enzyme inhibitors such as protease inhibitors due to their unique properties of the α -trifluoromethyl ketone functionality.^{1–5} The highly electron-withdrawing trifluoromethyl group in the α -position of the carbonyl facilitates the formation of tetrahedral hemiketals or hydrates with water. The tetrahedral hydrates interacts with protease, and inhibits the enzyme activity.¹ Some 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 These molecules have potential for radiolabeling with fluorine-18, and the labeled compounds can be used as marker for cell proliferation or viral infection.

TFMKs are traditionally prepared from inexpensive trifluoroacetic acid derivatives.^{7,8} Recently we reported the direct preparation of simple TFMKs from carboxylic esters with (trifluoromethyl)trimethylsilane (TMS-CF₃).⁹ This method has been further extended by others with CsF catalyzed trifluoromethylation of esters.¹⁰ However, these methods are not suitable for the synthesis of [¹⁸F]-labeled TFMKs since it is difficult to prepare [¹⁸F]-labeled trifluoroacetic acid derivatives or TMS-CF₃ due to the short half-life of ¹⁸F ($t_{1/2}$ = 110 min). Most recently, we have developed a simple and convenient general synthesis of α -trifluoromethyl ketones by fluorination using elemental fluorine F₂.¹¹ Herein, we report the first synthesis of [¹⁸F]-labeled TFMKs as model compounds by fluorination of 2,2-difluoro silyl enol ethers with radioactive fluorine [¹⁸F]-F₂.

Results and discussion

Compounds **1a–d** were prepared following the literature method¹² and modified in our laboratory.¹³ All compounds were identified by ¹H and ¹⁹F NMR spectroscopy and mass spectrometry, and found to be consistent with the literature data. These silyl enol ethers are much more stable towards hydrolysis compared to the normal silyl enol ethers, which enables the simple handling without decomposition. However, freshly prepared compounds were used for radiolabeling experiments.

Figure 1 represents the scheme for the [¹⁸F]-labeled synthesis of the α -trifluoromethyl ketones. Compounds **2a–d** were prepared by fluorination of **1a–d** with [^{18/19}F]-F₂. [^{18/19}F]-F₂ was produced in the cyclotron by bombardment of [¹⁸O]O₂ followed by mixing the target gas with non-radioactive F₂. The mixture of [^{18/19}F]-F₂ was bubbled into the solution

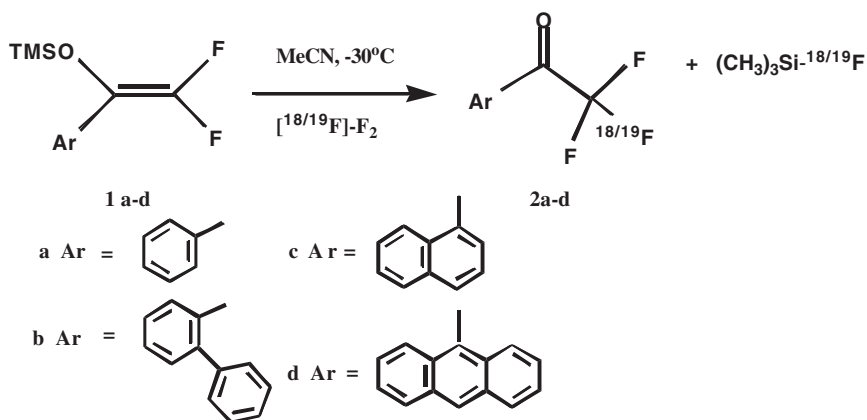


Figure 1. Synthetic Scheme of $[^{18}\text{F}]$ - α -trifluoromethyl ketones

of the substrate (**1a–d**) at low temperature for efficient trapping of activity. Trapping of activity was quite efficient for 2–3 mg ($\sim 10 \mu\text{mol}$) of the precursors. Since the syntheses were carrier added, a sufficient amount of F_2 was present, resulting in absence of any unreacted starting material in the reaction mixture.

The radiolabeled ketones could not be purified by HPLC since the products readily converted to the hydrated compound and eluted much earlier than the desired ketones. However, the radiolabeled ketones were purified by chromatography on a small silica gel column and eluted with the organic solvent mixture, ethyl acetate and hexane (10:90). Fractions (0.5 ml) were collected and radioactivity measured on a dose calibrator. The products were eluted in the earlier fractions with an r.f. value of approximately 0.8. Pure fractions after combining were analyzed by TLC and found to be co-eluted with authentic sample checked by both UV and radioactivity. Figure 2 is a representative radio TLC for the compound **2b**.

In non-radioactive preparations excess F_2 was used and the chemical yields were greater than 80%. However, in the radiochemical syntheses only 50% of the activity is incorporated into the substrate resulting lower yields in the range of 22–28% (d.c.) from the end of bombardment (EOB). The radiochemical purity was $>99\%$ with specific activities 15–20 GBq/mmol. The synthesis time was 35–40 min from the EOB. In a representative preparation of **2b**, 30 mCi of labeled product was obtained starting from 120 mCi of trapped activity $[^{18}\text{F}]\text{-F}_2$.

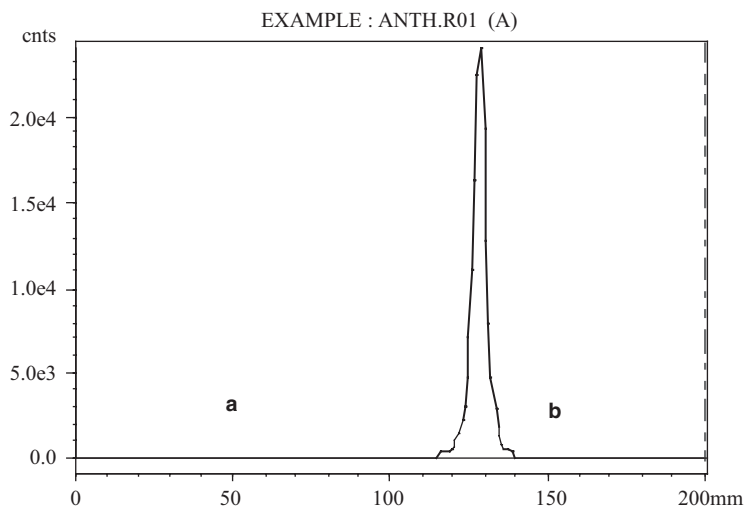


Figure 2. Radio TLC of 1-*n*-butylphenyl- α -trifluoromethyl ketone; a = point of application; b = solvent front

Experimental

Reagents and instrumentation

All reagents and solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI), and used without further purification, unless otherwise specified. Dichloromethane (CH_2Cl_2) and fluorotrichloromethane (CFCl_3) were distilled over calcium hydride (CaH_2), and acetonitrile (MeCN) was distilled over phosphorus pentoxide (P_2O_5) prior to use.

Proton, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 500 or 360 MHz NMR spectrometer in chloroform- D using tetramethylsilane and trichlorofluoromethane as internal standards, respectively. Mass spectra were obtained on a Hewlett Packard 5890 Gas Chromatograph equipped with a Hewlett Packard 5971 Mass Selective Detector.

Column chromatography was performed using silica gel (60–200 mesh) and ethyl acetate/hexane (10:90) as eluent. Thin layer chromatography (TLC) was performed on a silica gel plate ($1 \times 10 \text{ cm}^2$) and developed in the appropriate solvent system ethyl acetate/hexane (10:90). Radioactivity on the developed TLC plate was scanned on a TLC scanner (Bioscan Inc., Washington, DC) to obtain a radiochromatogram.

Preparation of 2,2-difluoro silyl enol ethers (1a–d)

All these 2,2-difluoro silyl enol ethers (**1a–d**) were prepared from the respective ketones via magnesium metal mediated reductive defluorination following a literature procedure,^{12,13} and a representative method is described. 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 (non-radioactive) **2a** (5.2 g, 30 mmol) was added dropwise into the flask via a syringe. After addition, the reaction mixture was stirred for an additional 1 h. The completion of the reaction was monitored by ¹⁹F NMR spectroscopy. The solvent and excess TMSCl were removed under vacuum, and hexane (50 ml) was added to the residue. Solid impurities were removed by suction filtration, and the solvent was evaporated to afford 2,2-difluoro-1-phenyl-1-trimethylsilyloxyethene **1a** (6.8 g, 99% yield). The product was characterized by ¹H and ¹⁹F NMR spectroscopy and mass spectrometry. Spectroscopic data were consistent with the literature.¹² Compounds **1b–d** were also characterized by ¹H and ¹⁹F NMR spectroscopy and mass spectrometry.

Preparation of [¹⁸F]- α -trifluoromethyl ketones (2a–d)

All experiments were performed under similar conditions, and a representative method is described. 2,2-Difluoro-1-phenyl-1-trimethylsilyloxy-ethene **1a** (2 μ l, 11 μ mol) was dissolved in dry acetonitrile (0.5 ml) and cooled to -45°C. A mixture of fluorine [^{18/19}F]-F₂ and nitrogen (F₂/N₂ (v/v = 1/8)) was bubbled into the solution for 10 min. Radioactivity was measured on a dose calibrator (Capintec Inc., Ramsey, New Jersey), and the reaction mixture was warmed to room temperature. The crude product was purified by chromatography on a silica gel column using 10% ethyl acetate in hexane as eluent. Fractions (0.5 ml) were collected and radioactivity measured. Fractions containing radioactivity were combined and solvent was evaporated to obtain the pure product. The product was analyzed by TLC with an authentic compound as reference. The TLC plate after development was scanned for radioactivity on a TLC scanner, checked under UV lamp and compared with the reference compound. Analysis of the TLC plate showed the material to be 99% pure. Radiochemical yield was 22% (d.c). Compounds **2b–d** were produced in similar radiochemical yields in the range of 22–28% (d.c).

Conclusion

A convenient synthesis of [^{18}F]-labeled- α -trifluoromethyl ketones has been developed. The radiochemical yield of this synthesis was 22–28% decay corrected (d.c.) from the EOB. The radiochemical purity was >99% and specific activity 15–20 GBq/mmol. The synthesis time was 35–40 min from the EOB. This method appears to be suitable for general syntheses of other biologically active [^{18}F]-labeled- α -trifluoromethyl ketones for PET imaging.

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References

1. Kawase M. *J Syn Org Chem Japan* 2001; **59**: 755.
2. Gelb MH, Svaren JP, Abales RH. *Biochemistry* 1985; **24**: 1813.
3. Takahashi LH, Radhakrishnan R, Rosenfield Jr RE, Meyer Jr EF. *Biochemistry* 1989; **28**: 7610.
4. Morris TS, Frommann S, Shechosky S, Lowe C, Lall MS, Gauss-Muller V, Purcell RH, Emerson SU, Vederas JC, Malcolm BA. *Bioorg Med Chem* 1997; **5**: 797.
5. Imperiali B, Abeles RH. *Biochemistry* 1986; **25**: 3760.
6. Kawase M, Sakagami H, Kusama K, Motohashi N, Saito S. *Bioorg Med Chem Lett* 1999; **9**: 3113.
7. Creary X. *J Org Chem* 1987; **52**: 5026.
8. Keumi T, Shimada M, Takahashi M, Kitajama H. *Chem Lett* 1990; 783.
9. Wiedemann J, Heiner T, Mloston G, Prakash GKS, Olah GA. *Angew Chem Int Ed* 1998; **37**: 820.
10. Singh RP, Cao G, Kirchmeier RL, Shreeve JM. *J Org Chem* 1999; **64**: 2873.
11. Prakash GKS, Hu J, Alauddin MM, Conti PS, Olah GA. *J Fluorine Chem* 2003; **121**: 239.
12. Amii H, Kobayashi T, Hatamoto Y, Uneyama K. *Chem Comm* 1999; 1323.
13. Prakash GKS, Hu J, Olah GA. *J Fluorine Chem* 2001; **112**: 357.