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Efficient synthesis of [^{18}F]trifluoromethane and its application in the synthesis of PET tracers†

Cite this: *Chem. Commun.*, 2013, **49**, 4018

Received 29th October 2012,
Accepted 25th March 2013

DOI: 10.1039/c3cc37833k

www.rsc.org/chemcomm

Dion van der Born,[a] J. (Koos) D. M. Herscheid,[a] Romano V. A. Orru[b] and Danielle J. Vugts*[ac]

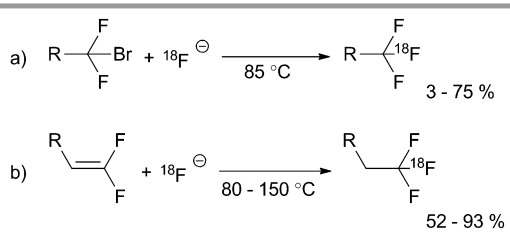
A new strategy towards [^{18}F]trifluoromethyl-containing compounds is developed. [^{18}F]trifluoromethane is synthesised in a fast and efficient manner and subsequently used in the reaction with aldehydes and ketones forming [^{18}F]trifluoromethyl carbinols in good yields.

Positron emission tomography (PET) is a powerful molecular imaging technique that can visualise biological processes *in vivo*.[1] Today, PET has proven to be a valuable tool for the detection, characterisation and monitoring of diseases and for the investigation of the efficacy of pharmaceuticals. Therefore, there is a continuous need for effective positron-emitting tracers that specifically interact in the biological processes of interest.[2]

The development of a PET-tracer usually starts from a known biologically active compound by replacing one of the carbon, nitrogen, oxygen or fluorine atoms by its radioactive isotope. Synthesis of such compounds is challenging due to the short physical half-life of these isotopes (^{11}C $t_{1/2}$ = 20 min, ^{13}N $t_{1/2}$ = 10 min, ^{15}O $t_{1/2}$ = 2 min, ^{18}F $t_{1/2}$ = 110 min). In general, the introduction of the isotope and subsequent purification and analysis of the tracer have to be finalized within 3 half-lives. Consequently, robust, reliable and rapid chemical procedures are essential for success.[3]

Many pharmaceuticals contain a trifluoromethyl (CF_3) functional group. The CF_3 group is incorporated into drug candidates to improve their binding selectivity, lipophilicity, and metabolic stability.[4] [^{18}F]CF_3-containing compounds are however rare because only limited synthetic approaches are available. Of the various fluorine-18 sources, only [^{18}F]fluoride is available at most cyclotron sites, and therefore reactions using this fluorine-18 source are especially of interest. Albeit, only a handful of procedures using nucleophilic [^{18}F]fluoride to prepare [^{18}F]trifluoromethylated compounds have been reported.[5,6] The published methods employ the direct reaction of [^{18}F]fluoride with electrophiles, like difluorobromomethyl- or *gem*-difluoroalkenyl containing compounds (Scheme 1). These methods do generate the [^{18}F]trifluoromethyl group in a single synthetic step, but with limited success. Simple substrates react in up to 93% yield, however, the labelling of more complex structures results in very low yields (<15%).[5] Moreover, precursors containing the difluorobromomethyl- or *gem*-difluoroalkenyl functional group are difficult to obtain using commercial sources or synthetic methods.

A major limitation of the reaction with the *gem*-difluoroalkenyl group is that it actually yields a [^{18}F]2,2,2-trifluoroethyl group. Trifluoromethyl aryls, for example, can therefore not be obtained *via* this method.



Scheme 1 Reported reactions of [^{18}F]fluoride with: (a) difluorobromomethyl[5] and (b) *gem*-difluoroalkenyl[6] precursors.

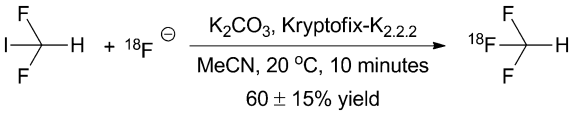
In this communication we present a novel approach to synthesise radiopharmaceuticals containing a CF_3 group *via* nucleophilic trifluoromethylation using [^{18}F]trifluoromethane.

During initial studies, we discovered that the reaction of difluoroiodomethane with [^{18}F]fluoride/kryptofix 2.2.2 in acetonitrile provided [^{18}F]trifluoromethane in a satisfactory 60 ± 15% yield in a reaction time of 10 minutes at room temperature (Scheme 2).

[^{18}F]trifluoromethane could be easily isolated by purging it out of the reaction mixture using a flow of helium. The gaseous [^{18}F]trifluoromethane was separated from any gaseous difluoroiodomethane precursor by passing it through a silica column and trapping the product in either DMF at −60 °C with a 88 ± 8% efficiency or in THF at −100 °C with a 96 ± 3% efficiency in

[a] *Department of Radiology and Nuclear Medicine, VU University Medical Center, PO Box 7057, 1007MB, Amsterdam, The Netherlands. E-mail: d.vugts@vumc.nl*
[b] *Department of Chemistry and Pharmaceutical Sciences, Amsterdam Institute for Medicines and Systems, VU University, De Boelelaan 1083, 1081HV, Amsterdam, The Netherlands*
[c] *Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, PO Box 7057, 1007MB, Amsterdam, The Netherlands*

† Electronic supplementary information (ESI) available: Synthesis and characterisation of reference compounds and experimental details. See DOI: 10.1039/c3cc37833k

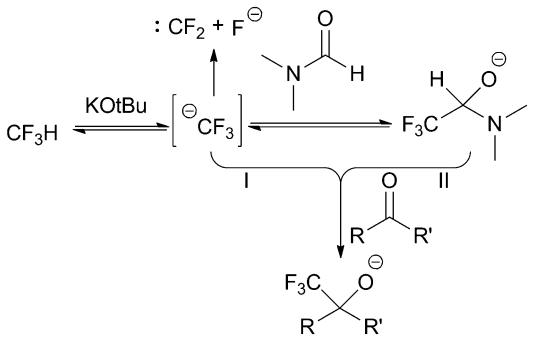


Scheme 2 Synthesis of [^{18}F]trifluoromethane.

3 minutes. HPLC analysis of the obtained [^{18}F]trifluoromethane solution showed no radioactive or UV-active impurities (see ESI†).

The time needed for the synthesis of [^{18}F]trifluoromethane, which includes azeotropic drying of [^{18}F]fluoride/kryptofix 2.2.2 and subsequent reaction and purification, is about 30 minutes. This provides enough time for a follow up reaction, and therefore the applicability of [^{18}F]trifluoromethane was further investigated.

In order to use [^{18}F]trifluoromethane in nucleophilic trifluoromethylations, it needs to be deprotonated first. It is known that deprotonation of "cold" trifluoromethane in THF yields a trifluoromethyl anion that decomposes to difluorocarbene and fluoride (Scheme 3).[7] Deprotonation in DMF, however, results in a trifluoromethyl anion stabilised as the corresponding *gem*-aminoalcoholate. Using this method, aldehydes and ketones undergo reactions with trifluoromethane to form the corresponding trifluorocarbinols in high yields.[7] The trifluoromethylation of a carbonyl group may proceed *via* two distinct pathways (Scheme 3). Either the trifluoromethyl anion attacks directly the electrophilic carbonyl group, where the *gem*-aminoalcoholate only acts as a temporary reservoir of the trifluoromethyl anion, or the *gem*-aminoalcoholate formed in DMF reacts with the carbonyl group.



Scheme 3 Reaction pathways of the trifluoromethyl anion.

When fluorine-18 is used in a reaction the resulting products and reactants can easily be monitored using HPLC and a radioactivity detector. With such an analytical set-up, reaction progress is easily followed and we decided to investigate the mechanism of trifluoromethylation of carbonyls using [^{18}F]trifluoromethane in more detail.

The reaction of [^{18}F]trifluoromethane and benzophenone was selected as a model reaction, because the initial experiments showed that benzophenone reacts cleanly with the corresponding [^{18}F]trifluorocarbinol **2a**. First the trifluoromethylation reaction using [^{18}F]trifluoromethane and KO*t*Bu (100 mM) (5 min at 20 °C) at various concentrations of benzophenone was investigated in THF that contained various percentages of DMF (Fig. 1a). Surprisingly, the reaction in neat THF yielded the desired product **2a** in up to 86%. However, to achieve this, a high concentration of benzophenone (500 mM) was required. This demonstrates that the trifluoromethyl anion can react directly with benzophenone (pathway I).

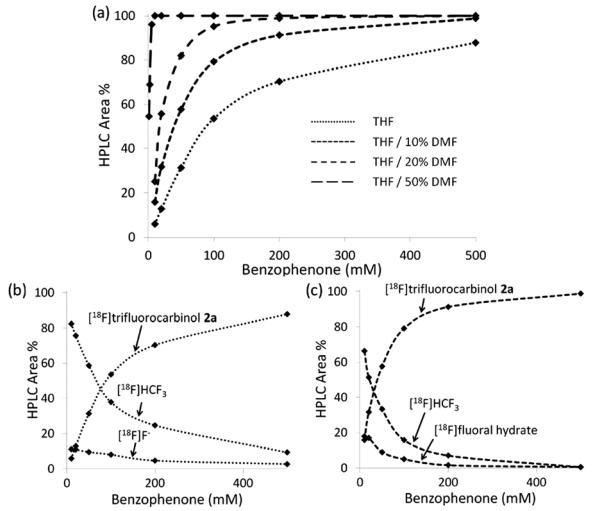
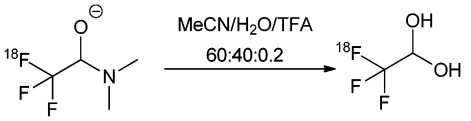


Fig. 1 Analysis of the reaction of [^{18}F]HCF_3 with benzophenone using radio-HPLC. (a) Investigation of the influence of the DMF concentration on the formation of [^{18}F]trifluorocarbinol **2a**; (b) determination of the reaction products in THF; (c) determination of the reaction products in THF with 10% DMF.



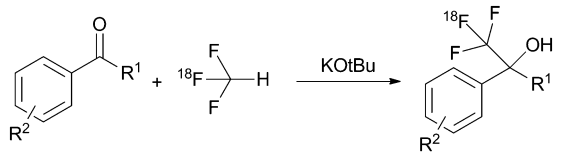
Scheme 4 Formation of [^{18}F]fluoral hydrate in the HPLC eluent.

However, at low benzophenone concentrations, the yield of **2a** decreased and decomposition of the trifluoromethyl anion led to the formation of [^{18}F]fluoride. In this case, the presence of 50% of DMF led to a tremendous increase in product yield. Apparently, the direct reaction pathway I is very slow at these concentrations and pathway II *via* the *gem*-aminoalcoholate comes more into play at increasing DMF concentrations. In these reactions, [^{18}F]fluoride was also not found as a by-product, but [^{18}F]fluoral hydrate was detected instead. This can be attributed to protonation of the *gem*-aminoalcoholate intermediate in the acidic HPLC eluent (Scheme 4) and therefore can be used to quantify the amount of *gem*-aminoalcoholate present in the reaction mixture.

The absence of [^{18}F]fluoride indicates that the *gem*-aminoalcoholate does not act as a trifluoromethyl anion reservoir, but reacts directly in a concerted reaction with the substrate. If the *gem*-aminoalcoholate is in equilibrium with the trifluoromethyl anion, at least some [^{18}F]fluoride should have been formed.

To investigate the scope of the [^{18}F]trifluoromethylation reaction discussed above various benzaldehydes **1**, acetophenones **3** and benzophenones **5** (for R^2 see Table 1–3) containing electron withdrawing and donating groups (Scheme 5) were selected as the electrophilic reaction partners.

Reaction with substituted benzophenones **1** provided the expected products in excellent yields (Table 1). The synthesis of [^{18}F]**2b** (R^2 = 4-OMe), [^{18}F]**2e** (R^2 = 4-NO_2) and [^{18}F]**2f** (R^2 = 3-NO_2) required although an increasing concentration of KO*t*Bu. Under the low yielding reaction conditions, unreacted [^{18}F]trifluoromethane was still present, because the substrates had degraded (as shown by UV-HPLC analysis).



R^1 = Ph (**1a-f**,[^{18}F]**2a-f**); CH_3 (**3a-f**,[^{18}F]**4a-f**); H (**5a-f**,[^{18}F]**6a-f**)

Scheme 5 [^{18}F]trifluoromethylation using [^{18}F]HCF_3.

Table 1 Trifluoromethylation of benzophenones **1**[a]

Entry	R^2	Substrate (μmol)	KO*t*Bu (μmol)	Product	Radiochemical conversion (%)
1	H	10	20	[^{18}F]**2a**	>99
2	4-OMe	10	20	[^{18}F]**2b**	16
3	4-OMe	10	30	[^{18}F]**2b**	>99
4	4-CF_3	10	20	[^{18}F]**2c**	99
5	4-F	10	20	[^{18}F]**2d**	>99
6	4-NO_2	10	20	[^{18}F]**2e**	1
7	4-NO_2	10	50	[^{18}F]**2e**	96
8	3-NO_2	10	20	[^{18}F]**2f**	30
9	3-NO_2	10	50	[^{18}F]**2f**	74

[a] Reaction conditions: 1 mL DMF, 20 °C, 5 minutes.

Table 2 Trifluoromethylation of acetophenones **3**[a]

Entry	R^2	Substrate (μmol)	KO*t*Bu (μmol)	Product	Radiochemical conversion (%)
1	H	100	150	[^{18}F]**4a**	41
2	4-OMe	100	150	[^{18}F]**4b**	44
3	4-CF_3	100	150	[^{18}F]**4c**	22
4	4-F	100	150	[^{18}F]**4d**	36
5	4-NO_2	100	150	[^{18}F]**4e**	0
6	3-NO_2	100	150	[^{18}F]**4f**	0

[a] Reaction conditions: 1 mL DMF, 80 °C, 5 minutes.

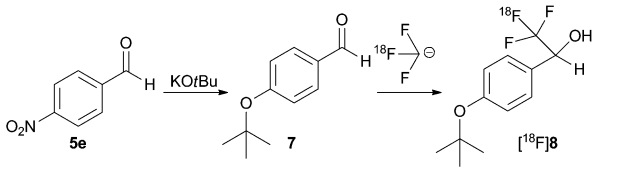
Table 3 Trifluoromethylation of benzaldehydes **5**[a]

Entry	R^2	Precursor (μmol)	KO*t*Bu (μmol)	Product	Radiochemical conversion (%)
1	H	10	20	[^{18}F]**6a**	97
2	4-OMe	10	20	[^{18}F]**6b**	98
3	4-CF_3	10	20	[^{18}F]**6c**	31
4	4-CF_3	10	50	[^{18}F]**6c**	43
5	4-CF_3	20	50	[^{18}F]**6c**	86
6	4-F	10	20	[^{18}F]**6d**	3
7	4-F	10	50	[^{18}F]**6d**	94
8	4-NO_2	10	20	[^{18}F]**6e**	0[b]
9	3-NO_2	10	20	[^{18}F]**6f**	2
10	3-NO_2	10	50	[^{18}F]**6f**	26
11	3-NO_2	20	50	[^{18}F]**6f**	90

[a] Reaction conditions: 1 mL DMF, 20 °C, 5 minutes. [b] Increasing KO*t*Bu or precursor amounts did not lead to increased yield.

High base concentrations probably led to faster deprotonation and reaction of [^{18}F]trifluoromethane with the substrates, before degradation of the substrate occurred.

In the case of acetophenones **3**, enolate formation was expected under the applied reaction conditions, which would lead to a decreased availability of reactive ketones. Indeed, higher base and precursor concentrations were required to obtain the products in satisfactory yields (Table 2).



Scheme 6 Major by-product formation in the reaction of **5e** with [^{18}F]HCF_3.

In these reactions, also no radioactive by-products were formed and in the synthesis of [^{18}F]**4e** (R^2 = 4-NO_2) and [^{18}F]**4f** (R^2 = 3-NO_2) only unreacted [^{18}F]trifluoromethane was observed. Substrate degradation, as was observed using UV-HPLC, caused by the strong basic conditions probably led to low yields.

Benzaldehydes **5** reacted in a moderate to high yield with [^{18}F]trifluoromethane (Table 3). Also here a positive effect of an increasing KO*t*Bu concentration on the product yield was observed. Most reactions did not yield by-products, except for the synthesis of [^{18}F]**6e**. In this case not [^{18}F]**6e**, but [^{18}F]**8** was formed (Scheme 6). This may be explained by nucleophilic attack of the *tert*-butoxide anion on the precursor 4-nitrobenzaldehyde **5e** (Scheme 6) resulting in 4-*t*-butoxy-benzaldehyde **7** which subsequently reacts with [^{18}F]trifluoromethane to form [^{18}F]1-(4-(*tert*-butoxy)phenyl)-2,2,2-trifluoroethanol **8**.

In summary, [^{18}F]trifluoromethane can be prepared in high yield in a short synthesis time and undergoes smooth reaction with various aromatic aldehydes and ketones to give [^{18}F]trifluoromethylcarbinols in reasonable to good yields. Substrate stability seems to be the most important factor to obtain high product yields.

We are currently investigating the use of [^{18}F]trifluoromethane towards other products (trifluoromethylthioethers, trifluoromethylarenes) and towards the synthesis of [^{18}F]TMSCF_3, a milder reagent for trifluoromethylation reactions.

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