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Research Article

Hydroacylation of 4-[^{18}F]fluorobenzaldehyde: a novel method for the preparation of 4′-[^{18}F]phenylketones

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Summary

To assess the potential of intermolecular hydroacylation reactions as a new fluorine-18 labeling method, model reactions of [^{18}F]fluorobenzaldehyde with three different olefins (1-hexene (**2a**), allylbenzene (**2b**), and 3-phenoxypropene (**2c**)) in the presence of Wilkinson's catalyst were performed. The procedure gave high radiochemical yields (38–62%) of [^{18}F]fluorophenylketones with short reaction times (15 min). The intermolecular hydroacylation reaction provides a new method for the preparation of fluorine-18 labeled compounds. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: hydroacylation; *p*-[^{18}F]fluorophenylalkyl ketone; F-18 labeling; [^{18}F]fluorobenzaldehyde; Wilkinson's catalyst; Positron emission tomography

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Introduction

Positron emission tomography (PET) is widely used as a basic tool for the medical imaging of the human body.[1] Fluorine-18 ($t_{1/2} = 110$ min) is a popular radionuclide for labeling biomolecules. Although fluorine-18 plays an important role in the field of biomedicinal chemistry, only few chemical reactions are suitable for the introduction of fluorine-18 to biomolecules with high specific radioactivity.[2–5] An adequate method for labeling of a molecule with fluorine-18 requires rapid, convenient and efficient[6] incorporation of the radionuclide into the molecule of interest. Although fluorine-18 labeled aliphatic compounds can be easily synthesized by nucleophilic substitution[7] on sulfonate esters or by halofluorination on olefins,[8–11] aromatic fluorides are more stable *in vivo* than aliphatic fluorides. In general, aromatic fluorides do not easily undergo metabolic defluorination *in vivo*, and therefore, it is desirable to introduce the fluorine-18 to the aromatic ring. There are a number of publications that describe these reactions, for example, the [^{18}F]fluoride ion displacement reaction of a leaving group on the aromatic ring with an electron withdrawing group, such as a carbonyl group, *ortho* or *para* to the leaving group. Another useful reaction is a fluoride ion displacement of (4-formylphenyl)trimethylammonium triflate (**4**), providing 4-[^{18}F]fluorobenzaldehyde (**1**).[12–14] This 4-[^{18}F]fluorobenzaldehyde can be used directly in the reductive amination, or after further modifications, such as reduction and iodonation to [^{18}F]fluorobenzyl iodide followed by *N*-alkylation.[15,16]

Hydroacylation is a useful method for the synthesis of ketones from aldehydes and olefins via C–H activation. Recently, Jun *et al.* developed a general method for intermolecular hydroacylation using a Rh^{I} complex and 2-amino-3-picoline as cocatalyst.[17–19] They observed a remarkable enhancement of the reactivity when both benzoic acid and aniline were used as additives. In the absence of both benzoic acid and aniline in the reaction, the yield of intermolecular hydroacylation of benzaldehyde and 1-hexene was less than 20% in 12 h, and the addition of aniline alone increased the yield to 60% in 12 h. Moreover, the presence of both additives increased the yield up to 98% within 1 h.

To assess the potential of intermolecular hydroacylation for the fluorine-18 labeling, the radiochemical syntheses of [^{18}F]fluorophenylketones from [^{18}F]fluorobenzaldehyde and three different olefins (1-hexene (**2a**), allylbenzene (**2b**), and 3-phenoxypropene (**2c**)) were evaluated.

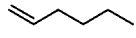
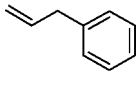
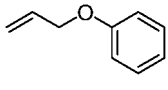
Results and discussion

*Hydroacylation reactions of olefin **2** with 4-fluorobenzaldehyde (cold reactions)*

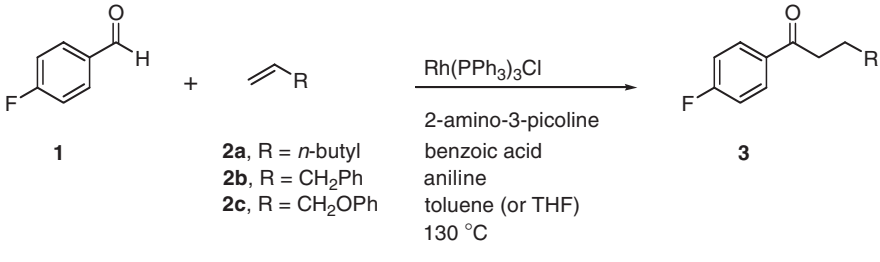
Hydroacylation reaction of model olefins with 4-fluorobenzaldehyde proceeded in moderate yield as summarized in Table 1 (Scheme 1).

At the tracer level, the solvent of choice for the preparation of 4-[^{18}F]fluorobenzaldehyde is dimethylsulfoxide (DMSO) as shown in Scheme 2. If the hydroacylation reaction would go well in DMSO, we would not have to change the solvent or to isolate 4-[^{18}F]fluorobenzaldehyde in the next hydroacylation step. However, we have found that the hydroacylation does not proceed in DMSO or acetonitrile, while toluene is known as the best solvent for hydroacylation reaction. When the hydroacylation reaction was carried out in one-tenth scale of the reactions in Table 1 while the solvent volume was kept the same (entry 1, Table 2), the yield dramatically dropped to 19%. Reoptimization of

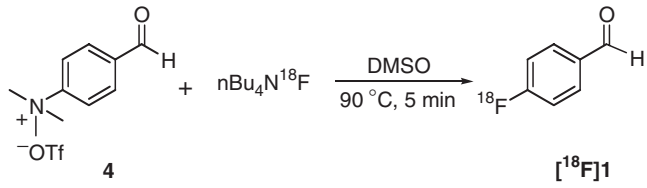
Table 1. Hydroacylation reactions of olefin 2 with 4-fluorobenzaldehyde in toluene or THF[a]

Entry	Olefins		Solvent	Yield (%)[b]
1		**2a**	Toluene	68[c]
2		**2a**	THF[d]	50
3		**2b**	Toluene	70[c]
4		**2b**	THF	58
5		**2c**	Toluene	85[c]
6		**2c**	THF	72

[a] *Reaction condition*: To a stirred solution of 4-fluorobenzylaldehyde (54 µl, 500 µmol), 2-amino-3-picoline (9.6 µl, 100 µmol), benzoic acid (3.8 mg, 30 µmol), aniline (27 µl, 300 µmol), and olefins (2500 µmol) in appropriate solvent (90 µl) was added $Rh(PPh_3)_3Cl$ (9 mg, 10 µmol) as a catalyst and the reaction mixture was heated at 130°C for 1 h.

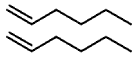
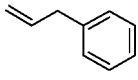
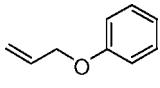


Scheme 1.



Scheme 2.

Table 2. Optimization of reactions of olefin 2 with 4-fluorobenzaldehyde in toluene or THF in diluted condition[a]

Entry	Olefins		Solvent	Yield (%)[b]
1[c]		**2a**	Toluene	19
2		**2a**	Toluene	40
3		**2a**	THF[d]	27
4		**2b**	Toluene	53
5		**2b**	THF	32
6		**2c**	Toluene	58[e]
7		**2c**	THF	40[e]

[a] *Reaction condition*: To a stirred solution of 4-fluorobenzaldehyde (5.3 µl, 50 µmol), 2-amino-3-picoline (2.9 µl, 30 µmol), benzoic acid (0.3 mg, 3 µmol), aniline (0.9 µl, 10 µmol), and olefins (250 µmol) in appropriate solvent (200 µl) was added $Rh(PPh_3)_3Cl$ (3.4 mg, 4 µmol) as a catalyst and the reaction mixture was heated at 130°C for 1 h.
[b] HPLC yields.
[c] This reaction was carried out in one-tenth scale of the reactions in Table 1 except solvent volume.
[d] Care should be taken while using THF at high temperature.
[e] Reaction was carried out for 45 min.

the hydroacylation reaction was thus made and smaller amounts of 4-fluorobenzaldehyde (50 µmol) were sufficient to give the same yield of the product as with the large amounts of the aldehyde (Table 2).

Hydroacylation reaction of 4-[^{18}F]fluorobenzaldehyde with olefins **2** *(hot reactions)*

In radiotracer experiments, the preparation of 4-[^{18}F]fluorobenzaldehyde (**[^{18}F]1**) was achieved by the nucleophilic aromatic substitution of (4-formylphenyl)-trimethylammonium triflate by [^{18}F]fluoride ion in DMSO at 90°C within 5 min in an overall 90% yield as shown in Scheme 2. **[^{18}F]1** was characterized by radio-TLC and separated by C-18 cartridge.[14] The isolated **[^{18}F]1** was used for intermolecular hydroacylation of three different olefins using Wilkinson's catalyst with other

Table 3. Hydroacylation reaction of 4-[^{18}F]fluorobenzaldehyde with olefins 2[a]

Entry	Olefin	Radiochemical field (%)[b] Toluene[c]	THF[c]
1	**2a**	38 ± 6.7 (3)[d]	30 ± 2.1 (3)
2	**2b**	47 ± 1.6 (3)	33 ± 7.9 (3)
3	**2c**	62 ± 4.5 (3)	44 ± 6.2 (3)

[a] Typical hydroacylation reaction was carried out in a sealed vial. A solution of 4-[^{18}F]fluorobenzaldehyde (40–50 μCi), 2-amino-3-picoline (5 μl, 52 μmol), benzoic acid (1.5 mg, 12 μmol), aniline (1.5 μl, 19 μmol), olefine (165 μmol), toluene (or THF 100 μl) and $Rh(PPh_3)_3Cl$ (2 mg, 2.3 μmol) was heated for 15 min at 110°C and then cooled. In the case of involving further characterization, the product was purified by HPLC.
[b] Average yield (%) measured by radio-TLC.
[c] Volume of the solvent was 100 μl.
[d] Number of reactions.

cocatalysts listed in Scheme 1. The progress of the reaction was monitored by radio-TLC. Surprisingly, the acylation has been achieved within 15 min only at 110°C, while Jun *et al.*[19] reported the hydroacylation with benzaldehyde and 1-hexene in 45–60 min at 130°C (Table 3). The radiochemical yield of the hydroacylated product was not improved after 15 min, except the formation of some side products.

Because **[^{18}F]1** is volatile and DMSO is not easily removed, a one-pot synthesis was attempted in THF. The radiochemical yields of **[^{18}F]1** varied from 5 to 50%, and unknown compounds appeared during hydroacylation in THF. Therefore, DMSO was used for preparation of 4-[^{18}F]fluorobenzaldehyde.

The maximum yield of hydroacylation was obtained in toluene rather than in THF. The reason may be that THF is more polar solvent that can make weak interaction with metal ion. The resulting competition between olefin and THF seems to be responsible for the low yield. The radiochemical yields of hydroacylations ranged from 30 to 62% (decay corrected). The yield was the highest in the reaction of 3-phenoxypropene and **1** or **[^{18}F]1**. This may be due to electron donating property of the phenoxide group that makes the reaction more feasible compared to entries 1 and 2 (Table 3). Authenticity of the radiolabeled products, **3a–c** was confirmed by coinjection with the unlabeled authentic samples by HPLC.

In conclusion, the efficient coupling of 4-[^{18}F]fluorobenzaldehyde with three alkenes was carried out in good radiochemical yield under mild reaction conditions with a short reaction time. Intermolecular hydroacylated products **3a–c** were obtained with 10–15% isolated yield

(decay corrected from EOB) and the total time of synthesis was 60 min from EOB. This reaction may be useful for the introduction of [^{18}F]fluorophenyl group to a variety of compounds.

Experimental

Materials and methods

All chemicals used were of reagent grade. Anhydrous solvents were dried over a proper drying agent and used freshly distilled. The products were separated by column chromatography using Merck silica gel (mesh size 230–400 ASTM). ^{1}H NMR spectra were obtained on Varian Gemini-400 or 200 (Palo Alto, CA, USA) and ^{13}C NMR spectra at 100 or 50 MHz. Chemical shifts were reported in parts per million (ppm, δ units). Chemical Ionization (CI) mass spectra were obtained on a GC/MS QP5050A spectrometer (Shimadzu, Kyoto, Japan). [^{18}F]Fluoride ion was prepared form [^{18}O]H_2O (Rotem Industries, Ltd., Israel) as described previously[20] in the PETtrace cyclotron (GEMS, Uppsala, Sweden). High performance liquid chromatography (HPLC) was carried out on a Thermo Separation Products System (Fremont, CA, USA) with a semipreparative column (Alltech Econosil silica gel, 10 μm, 10 × 250 mm). The eluant was simultaneously monitored by a UV detector (254 nm) and a NaI(Tl) radioactivity detector. Thin layer chromatography (TLC) was performed on Merck F_{254} silica plates and a Bioscan radio-TLC scanner (Washington DC, USA) was used for radio-TLC.

1-(4-Fluorophenyl)heptan-1-one ***(3a)***. A screw caped vial charged with 4-fluorobenzaldehyde (54 μl, 0.5 mmol), 2-aminopicoline (10 μl, 0.1 mmol), benzoic acid (3 mg, 0.03 mmol), aniline (27 μl, 0.3 mmol), 1-hexene (210 μl, 2.5 mmol) and toluene/THF (90 μl) was stirred for a few minutes. $Rh(PPh_3)_3Cl$ (9 mg, 0.01 mmol) was added into the reaction mixture and the whole reaction mixture was heated with stirring at 130°C for 1 h. After cooling the reaction mixture to room temperature, the product **3a** was isolated by flash column chromatography using hexane:ethyl acetate (4:1 mixture) as a white solid: m.p. 33.3–35.3°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, $J = 6.2$ Hz, 3 H), 1.25–1.33 (m, 6 H), 1.60–1.80 (m, 2 H), 2.93 (t, $J = 7.4$ Hz, 2 H), 7.07–7.16 (m, 2 H), 7.94–8.01 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.9, 165.7 (d, $J = 252.6$ Hz), 133.6, 130.6 (d, $J = 9.1$ Hz), 115.6

(d, $J = 21.6$ Hz), 38.6, 31.7, 29.0, 24.4, 22.5, 14.0; MS(CI) *m/z* 209.2 ($M^+ + 1$, 100), 138, 123, 113. HRMS (EI) *m/z* $C_{13}H_{17}FO$ (M^+) calcd: 208.1263; found: 208.1265.

1-(4-Fluorophenyl)-4-phenylbutan-1-one ***(3b)***. The synthesis procedure is same as for (**3a**) except allylbenzene (2.5 mmol, 330 µl): White solid; m.p. 49.2–50.3°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.03–2.11 (m, 2 H), 2.72 (t, $J = 7.3$ Hz, 2 H), 2.95 (t, $J = 7.3$ Hz, 2 H), 7.06–7.29 (m, 7 H), 7.90–7.97 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 165.5 (d, $J = 253.0$ Hz), 141.6, 133.4, 130.6 (d, $J = 9.1$ Hz), 128.5, 128.4, 126.0, 115.6 (d, $J = 22.0$ Hz), 37.5, 35.1, 25.6; MS(CI) *m/z* 243 ($M^+ + 1$, 100). HRMS (EI) *m/z* $C_{16}H_{15}FO$ (M^+) calcd: 242.1107; found: 242.1101.

1-(4-Fluorophenyl)-4-phenoxybutan-1-one ***(3c)***. The synthesis procedure is same as for (**3a**) except allyl phenyl ether (2.5 mmol, 342 µl) and reaction was heated for 45 min: White solid; m.p. 59.4–61.2°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.16–2.30 (m, 2 H) 3.18 (t, $J = 7.1$ Hz, 2 H), 4.07 (t, $J = 5.8$ Hz, 2 H), 6.87–7.31 (m, 7 H), 7.97–8.04 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 165.7 (d, $J = 253.2$ Hz), 158.8, 133.4, 130.6 (d, $J = 9.8$ Hz), 129.5, 120.7, 115.7 (d, $J = 21.2$ Hz), 114.4, 66.7, 34.9, 23.8; MS(CI) *m/z* 259 ($M^+ + 1$), 193, 165 (100), 95. HRMS (EI) *m/z* $C_{16}H_{15}FO_2$ (M^+) calcd: 258.1056; found: 258.1059.

General procedure for hydroacylation reaction of olefins with 4-fluorobenzaldehyde in diluted condition. To a stirred solution of 4-fluorobenzaldehyde (5.3 µl, 50 µmol), 2-aminopicoline (2.9 µl, 30 µmol), benzoic acid (0.3 mg, 3 mmol), aniline (0.9 µl, 10 µmol) and olefins (250 µmol), toluene/THF (200 µl), $Rh(PPh_3)_3Cl$ (3.4 mg, 4 µmol). The whole reaction mixture was heated with stirring at 130°C for 45 min to 1 h. After removal of solvent and addition of hexane, the catalyst was removed by filtration. The product was analyzed by HPLC.

General procedure for hydroacylation reaction of 4-[^{18}F]fluorobenzaldehyde with olefins. 4-[^{18}F]Fluorobenzaldehyde (**[^{18}F]1**) was obtained from (4-formylphenyl)trimethylammonium triflate (**4**) and no-carrier-added [^{18}F]F^- in DMSO (90 °C, 5 min). The [^{18}F]fluoride ion was resolubilized with THF (300 µl) and transferred to a glass vial containing (4-formylphenyl)trimethylammonium triflate (**4**, 2 mg, 6.4 µmol). The resolubilization procedure took 10–15 min with 85% yield.[21] **[^{18}F]1** was separated by C-18 cartridge in either toluene (or THF). Typical hydroacylation reaction was carried out in a sealed vial. A solution of 4-[^{18}F]fluorobenzaldehyde (1.48–1.85 MBq), 2-aminopicoline (5 µl, 52 µmol), benzoic acid (1.5 mg, 12 mmol), aniline (1.5 µl,

19 μmol) and olefins (165 μmol), toluene/THF (100 μl), $Rh(PPh_3)_3Cl$ (2 mg, 2.3 μmol) was heated for 15 min at 110°C and cooled. Product was checked by radio TLC and was purified using radio HPLC. Purification of F-18 labeled products were carried out on a HPLC column (Alltech Econosil silica gel, 10 μ, 250 × 10 mm) eluted with a 80:20 hexane:CH_2Cl_2 at a flow 4 ml/min. Authenticity of the products were confirmed by coelution with unlabeled standards on HPLC: **3a**, $R_t = 12.3$ min, $k' = 1.73$; **3b**, $R_t = 20.2$ min, $k' = 3.51$; **3c**, $R_t = 33.5$ min, $k' = 6.61$.

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