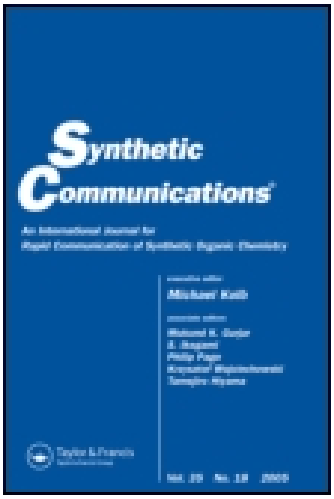


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Solid-Phase Nucleophilic Fluorination

Yosuke Demizu [a], Kaichi Sano [a b], Naoki Terayama [a], Wataru Hakamata [a], Yukiko Sato [a], Hideshi Inoue [b], Haruhiro Okuda [a] & Masaaki Kurihara [a]

[a] Division of Organic Chemistry, National Institute of Health Sciences, Tokyo, Japan

[b] Laboratory of Molecular Biochemistry, School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan

Accepted author version posted online: 17 Oct 2011.Published online: 27 Feb 2012.

To cite this article: Yosuke Demizu, Kaichi Sano, Naoki Terayama, Wataru Hakamata, Yukiko Sato, Hideshi Inoue, Haruhiro Okuda & Masaaki Kurihara (2012) Solid-Phase Nucleophilic Fluorination, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:12, 1724-1730, DOI: 10.1080/00397911.2010.535950

To link to this article: http://dx.doi.org/10.1080/00397911.2010.535950

Synthetic Communications®, 42: 1724–1730, 2012

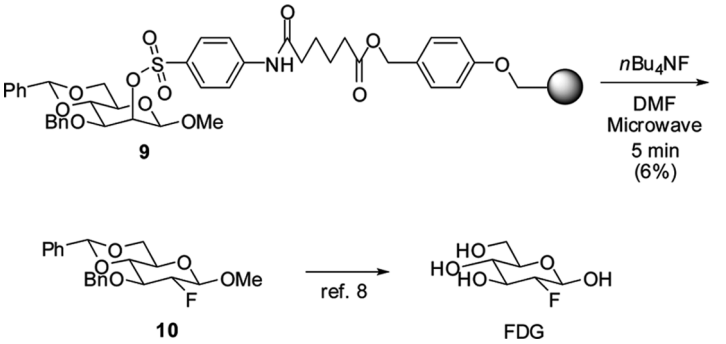
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.535950

SOLID-PHASE NUCLEOPHILIC FLUORINATION

Yosuke Demizu,[1] Kaichi Sano,[1,2] Naoki Terayama,[1] Wataru Hakamata,[1] Yukiko Sato,[1] Hideshi Inoue,[2] Haruhiro Okuda,[1] and Masaaki Kurihara[1]

[1]*Division of Organic Chemistry, National Institute of Health Sciences, Tokyo, Japan*
[2]*Laboratory of Molecular Biochemistry, School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan*

GRAPHICAL ABSTRACT



Abstract *This study demonstrates solid-phase nucleophilic fluorination. Polymer-bound 1-phenoxy-2-sulfonyloxyethane, as a model compound, is converted to a fluorinated compound in a short time. Furthermore, this method is applied to synthesize a precursor of 2-deoxy-2-fluoro-D-glucose by solid-phase synthesis using a microwave oven.*

Keywords FDG; fluorination; microwave; solid-phase synthesis

INTRODUCTION

Organofluorine compounds are important building blocks in medicinal, pharmaceutical, and agrochemical industries. In particular, ^{18}F compounds are useful for positron emission tomography (PET), which is an advanced biofunctional imaging method for clinical diagnosis and uses very short half-life radioisotopes.[1] 2-Deoxy-2-fluoro-D-glucose ([^{18}F]FDG) is the best clinically known and the most successful commercial PET radiopharmaceutical developed so far.[2] Several drugs

Received August 31, 2010.
Address correspondence to Masaaki Kurihara, Division of Organic Chemistry, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya, Tokyo 158-8501, Japan. E-mail: masaaki@nihs.go.jp

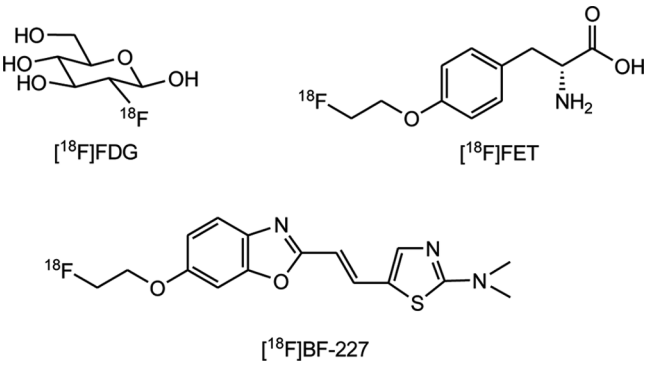


Figure 1. Examples of PET drugs.

have been developed for PET imaging of cancer cells and β-amyloid plaques in Alzheimer's disease. Some examples of labeled drugs for PET are shown in Fig. 1.[3] The synthesis of labeled drugs for PET involves various difficult issues. First, a very rapid process of synthesis and purification is required to allow for the 110-min half-life of ^{18}F. Second, synthesis must be performed using an automated device to avoid radiation exposure.

The recent solid-state synthesis of FDG by Brown et al.[4] prompted us to describe a rapid solid-phase nucleophilic fluorination (Fig. 2).[5,6] Solid-phase synthesis has various advantages: Unreacted compounds are bound to the resin and only fluorinated compounds are released from the resin, purification is straightforward, and solid-phase reagents are handled and stored easily. Furthermore, solid-phase synthesis is a suitable for an automated device.

Polymer-bound 1-phenoxy-2-sulfonyloxyethane **2**, which contains part of the structure of FET and BF-227, was synthesized as follows (Scheme 1): Polymer-bound sulfonyl chloride (70–90 mesh, loading 2.5 mmol/g, 1% cross-linked with divinylbenzene, **1**) was packed in a MacroKan reactor and treated with Et_3N and 2-phenoxyethanol in CH_2Cl_2 at room temperature for 4 days. The MacroKan reactor was washed with MeOH and CH_2Cl_2 to afford compound **2**.

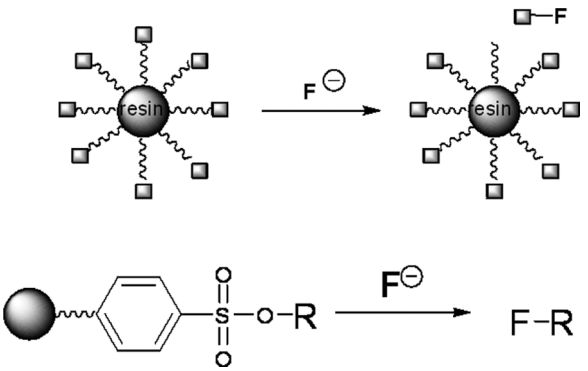
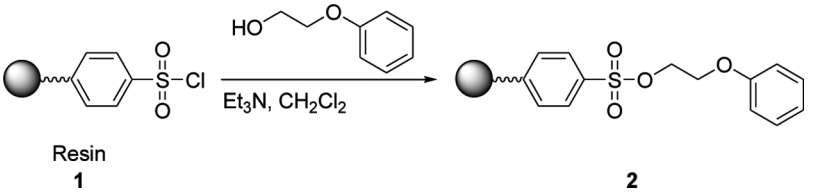


Figure 2. Solid-phase fluorination.

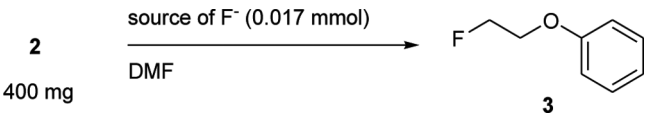


Scheme 1. Loading 2-phenoxyethanol on resin **1**.

Compound **2** in a MacroKan reactor was treated with a fluorination reagent under several conditions. The results are summarized in Table 1. The reaction was stopped for 30 min, and after the usual workup, only the desired product **3**[7] was obtained in 17% yield (entry 1). The yield of **3** from NH_4F was somewhat reduced as compared with nBu$_4$NF (entry 2). Although the use of KF gave **3** in a yield similar to that of nBu$_4$NF, it was required for the addition of cryptand (Kryptfix 222) to dissolve in dimethylforamide (DMF) (entry 3). A higher temperature gave a better yield (entries 4 and 5), and sufficient reaction time gave a good yield (entry 6).

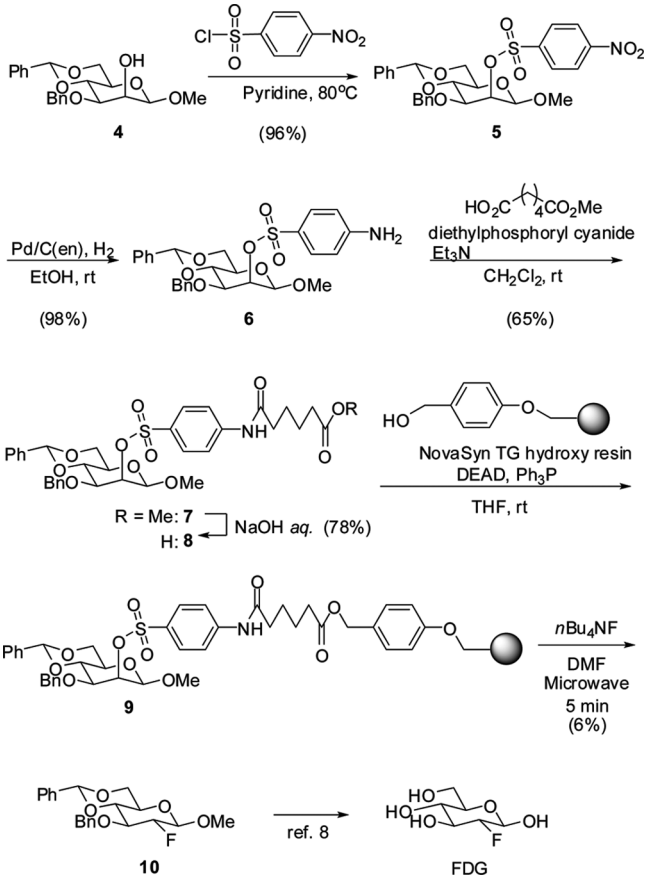
Next, we attempted to synthesize the precursor **10** of FDG by solid-phase synthesis. Mannose derivative **4**[8] bound to polymer-bound sulfonyl chloride **1** did not react with fluorination reagents under any conditions. Therefore, compound **9** was synthesized with a long linker as a new solid-bound mannose derivative (Scheme 2). The synthesis of **9** from mannose derivative **4** was as follows: Compound **4** was treated with 4-nitrobenzenesulfonyl chloride to afford sulfonylated **5** followed by reduction of the aromatic nitro group, and compound **6** was obtained. Linker was introduced by coupling **6** with monomethyl adipate followed by alkaline hydrolysis, and polymer-supported sugar **9** was finally obtained by the reaction of **8** with NovaSyn TG hydroxyl resin by the Mitsunobu reaction. The rapid solid-phase fluorination of **9** was performed with nBu$_4$NF assisted with a microwave oven at 200 °C for 5 min, and a fluorinated product **10** was obtained with 6% yield (estimated based on the amount of nBu$_4$NF). The yield of solid-phase fluorination seemed to be somewhat low; however, this method gave only the desired product **10** without the need

Table 1. Solid-phase fluorination of model compound **2**



Entry	Source of F^-	Time (h)	Temp. (°C)	Yield (%)[a]
1	nBu$_4$NF	0.5	100	17
2	NH_4F	0.5	100	12
3	KF[b]	0.5	100	18
4	nBu$_4$NF	0.5	50	7
5	nBu$_4$NF	0.5	150	79
6	nBu$_4$NF	6	100	>99

[a]Estimated based on the amount of fluorination reagent using HPLC analysis.
[b]Cryptand (Kryptfix 222) was added.



Scheme 2. Solid-phase fluorination of FDG precursor.

for further purification[8] and was suitable for practical applications. Nucleophilic fluorination of 2-sulfonlyoxy mannose derivative leads to an undesired product; see Ref. 8. Treatment of **10** with acid gave FDG.[8]

The results show this is a practical method for solid-phase nucleophilic fluorination. 1-Phenoxy-2-sulfonyloxyethane bound to a polymer was efficiently fluorinated to compound **3**. The solid-phase fluorination of mannose derivative **9** afforded FDG precursor **10** with high purity without further purification. Development of an automatic synthesis system for solid-phase fluorination and the use of an [^{18}F]-fluoride source are under way.

EXPERIMENTAL

Typical Procedure for Fluorination of Compound 2

Under an inert atmosphere, compound **2** (400 mg) was added to a solution of nBu$_4$NF (9.0 mg, 0.034 mmol) in DMF (20 mL) and then stirred for 30 min at 150 °C.

The solution was poured into water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford **3** (3.8 mg, 79% yield) without the need for further purification.

Methyl-3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-nitrobenzenesulfonyl-β-D-mannopyranoside (5). *p*-Nitrobenzenesulfonyl chloride (0.47 g, 2.12 mmol) was added to a solution of alcohol **4** (0.4 g, 1.06 mmol) in dry pyridine (10 ml), and stirred at 80 °C for 24 h. The reaction mixture was neutralized with 1 M aqueous HCl and then extracted with EtOAc. The organic phase was washed with brine solution, dried over Na_2SO_4, and concentrated in vacuo, and the resulting residue was purified by column chromatography (SiO_2, hex/EtOAc = 2/1) to afford the sulfonate **5** (0.57 g, 96%).

^{1}H NMR (400 MHz, $CDC1_3$) δ 3.37 (dd, $J = 4.8$, 10.0 Hz, 1H), 3.45 (s, 3H), 3.77 (dd, $J = 3.2$, 9.6 Hz, 1H), 3.86 (d, $J = 10.4$ Hz, 1H), 3.94 (m, 1H), 4.32 (dd, $J = 4.8$, 10.4 Hz, 1H), 4.51 (d, $J = 1.2$ Hz, 1H), 4.69–4.77(m, 2H), 5.25 (dd, $J = 1.2$, 3.2 Hz, 1H), 5.58 (s, 1H), 7.29–7.47 (m, 10H), 8.05–8.15 (m, 4H); ESI-MS: m/z: 580 $[M + Na]^+$.

Methyl-3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-aminobenzenesulfonyl-β-D-mannopyranoside (6). Encapsulated palladium on carbon (0.23 g, 3.9% loading) was added to a solution of **5** (0.30 g, 0.54 mmol) in EtOH (30 ml) under an atmosphere of hydrogen gas. The mixture was stirred for 2 h before filtering through celite. The solvent was removed in vacuo, and the crude product was purified by column chromatography (SiO_2, hex/EtOAc = 2/3) to furnish the product **6** (0.28 g, 98%).

^{1}H NMR (400 MHz, $CDC1_3$) δ 3.34 (ddd, $J = 4.8$, 10.0, 14.4 Hz, 1H), 3.46 (s 3H), 3.71 (dd, $J = 3.2$, 10.0 Hz, 1H), 3.85 (d, $J = 10.0$ Hz, 1H), 3.94 (dd, $J = 10.0$, 14.4 Hz, 1H), 4.09 (s, 2H), 4.28 (dd, $J = 4.8$, 10.0 Hz, 1H), 4.45 (d, $J = 0.8$ Hz, 1H), 4.70–4.83 (m, 2H), 5.21 (dd, $J = 0.8$, 3.2 Hz, 1H), 5.56 (s, 1H), 6.56–6.59 (m, 2H), 7.30–7.48 (m, 10H) 7.72–7.74 (m, 2H); ESI-MS: m/z: 550 $[M + Na]^+$.

Methyl-3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-(6-methoxy-6-oxohexanamido)benzenesulfonyl-β-D-mannopyranoside (7). Methyl hydrogen adipate (210 µl, 1.47 mmol), diethylphosphoryl cyanide (240 µl, 1.49 mmol), and Et_3N (415 µl, 2.97 mmol) were added to a solution of alcohol **6** (0.26 g, 0.49 mmol) in dry CH_2Cl_2 (15 ml), and stirred at room temperature for 21 h before the addition of saturated aqueous NaCl (10 mL) to quench. The reaction mixture was extracted with EtOAc, the combined organic extract was washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified via column chromatography (SiO_2, hex/EtOAc = 2/3) to afford the product **7** (0.21 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68–1.81 (m, 4H), 2.40 (m, 4H), 3.33 (ddd, $J = 5.2$, 9.6, 10.4 Hz, 1H), 3.43 (s, 3H), 3.70 (dd, $J = 3.6$, 9.6 Hz, 1H), 3.69 (s, 3H) 3.84 (m, 1H), 3.94 (m, 1H), 4.28 (m, 1H), 4.45 (d, $J = 1.2$ Hz, 1H), 4.70–4.80 (m, 2H), 5.21 (m, 1H), 5.56 (s, 1H), 7.28–7.92 (m, 15H); ESI-MS m/z 692 $[M + Na]^+$.

Methyl-3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-(5-carboxypentanamido)-benzenesulfonyl-β-D-mannopyranoside (8). Aqueous NaOH 1 M, (12 ml) was added to a solution of **7** (0.43 g, 0.64 mmol) in MeOH and stirred at room temperature for 2 h. The mixture was neutralized with 1 M aqueous HCl (15 ml) and

extracted with EtOAc, the combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified via column chromatography (SiO_2, CH_2Cl_2/MeOH = 10/1) to afford the product **8** (0.33 g, 78%).

^{1}H NMR (400 MHz, $CDC1_3$) δ 1.71–1.85 (m, 4H), 2.43 (m, 4H), 3.33 (ddd, J = 4.8, 9.6, 10.4 Hz, 1H), 3.43 (s, 3H), 3.71 (dd, J = 3.2, 9.6 Hz, 1H), 3.84 (m, 1H), 3.94 (m, 1H), 4.28 (m, 1H), 4.45 (d, J = 1.2 Hz, 1H), 4.70–4.80 (m, 2H), 5.21 (m, 1H), 5.56 (s, 1H), 7.28–7.91 (m, 15H), 9.02 (br s, 1H); ESI-MS m/z: 654 $[M - H]^-$.

Coupling of Acid 8 to NovaSyn TG Hydroxy Resin

PPh_3 (0.18 g, 0.7 mmol) and diethyl acetylenedicarboxylate (DEAD, 1.26 ml, 2.8 mmol) were added to a hydroxy resin (NovaSyn TG hydroxy resin, 200-400 mesh, loading 0.64 mmol/g, 1.09 g) and acid **8** in THF (10 ml). The reaction was stirres gently under Ar gas at rt for 14 h. The resin was removed by filtration; washed with THF (3 × 10 ml), DMF (3 × 10 ml), EtOH (3 × 10 ml), Et_2O (3 × 10 ml); and dried in vacuo at rt for 24 h.

Methyl-3-*O*-benzyl-4,6-*O*-benzylidene-2-fluoro-β-D-glucopyranoside (10). Under an inert atmosphere, compound **9** (120 mg) and nBu$_4$NF (42.7 mg, 0.167 mmol) in DMF (1 mL) were put into a 2-ml reaction tube sealed by the rubber stopper, and then MW irradiation was carried out for 5 min at 200 °C. The solution was poured into water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford **10** (3.7 mg, 6% yield) without the need for further purification.

^{1}H NMR (400 MHz, $CDC1_3$) δ 3.59 (s, 3H), 3.49–3.94 (m, 4H), 4.34 (d, J = 7.8 Hz, 1H), 4.38 (dd, J = 4.6, 10.0 Hz, 1H), 4.49 (d, J = 2.0 Hz, 1H), 4.86 (s, 2H), 5.56 (s, 1H), 7.27–7.55 (m, 10H); ESI-MS m/z: 375 $[M + H]^+$.

ACKNOWLEDGMENT

This work was supported in part by the Budget for Nuclear Research of the Ministry of Education, Culture, Sports, Science, and Technology, based on screening and counseling by the Atomic Energy Commission.

REFERENCES

1. (a) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501–1516; (b) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, *17*, 2853–2873.
2. For recent reviews for [^{18}F]FDG, see (a) Wienhard, K. *Methods* **2002**, *27*, 218–225; (b) Mosconi, L. *Eur. J. Nucl. Med. Molec. Imaging* **2005**, *32*, 486–509; (c) Muylle, K.; Castaigne, C.; Flamen, P. *Curr. Opin. Oncol.* **2005**, *17*, 249–253; (d) Quon, A.; Gambhir, S. S. *J. Clin. Oncol.* **2005**, *23*, 1664–1673.
3. (a) Haradahira, T.; Maeda, M.; Kojima, M. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 497–507; (b) Wester, H. J.; Herz, M.; Weber, W.; Heiss, P.; Senekowitsch-Schmidtke, R.; Schwaiger, M.; Stöcklin, G. *J. Nucl. Med.* **1999**, *40*, 205–212; (c) Kudo, Y.; Okamura, N.; Furumoto, S.; Tashiro, M.; Furukawa, K.; Maruyama, M.; Itoh, M.; Iwata, R.; Yanai, K.; Arai, H. *J. Nucl. Med.* **2007**, *48*, 553–561.

4. (a) Brown, L. J.; Ma, N.; Bouvet, D. R.; Champion, S.; Gibson, A. M.; Hu, Y.; Jackson, A.; Khan, I.; Millot, N.; Topley, A. C.; Wadsworth, H.; Wynn, D.; Brown, R. C. D. *Org. Biomol. Chem.* **2009**, *7*, 564–575; (b) Brown, L. J.; Bouvet, D. R.; Champion, S.; Gibson, A. M.; Hu, Y.; Jackson, A.; Khan, I.; Ma, N.; Millot, N.; Wadsworth, H.; Brown, R. C. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 941–944.
5. (a) Bejot, R.; Fowler, T.; Carroll, L.; Boldon, S.; Moore, J. E.; Declerck, J.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2009**, *48*, 586–589; (b) Wiehn, M. S.; Lindell, S. D.; Bräse, S. Fluorinating cleavage of solid phase linkers. *Angew. Chem. Int. Ed.* **2008**, *47*, 8120–8122.
6. Kurihara, M.; Hakamata, W.; Okuda, H. *Jpn. Kokai Tokkyo Koho* JP200731647, 2007.
7. Viet, N.; Cheng, X.; Morton, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 7127–7132.
8. Haradahira, T.; Maeda, M.; Kai, Y.; Omae, H.; Kojima, M. *Chem. Pharm. Bull.* **1985**, *33*, 165–172.