A RAPID SYNTHESIS OF 2-DEOXY-2-FLUORO-D-GLUCOSE FROM XENON DIFLUORIDE SUITABLE FOR LABELLING WITH ^{18}F

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SUMMARY

A rapid synthesis of 2-deoxy-2-fluoro-D-glucose (3) from xenon difluoride is described. Reaction of 3,4,6-tri-O-acetyl-D-glucal (1) with xenon difluoride in ethyl ether in the presence of $BF_3 \cdot OEt_2$ for 20 minutes gave 2-deoxy-2-fluoro-3,4,6-tri-O-acetyl-D-glucopyranosyl fluoride (2) in 70-80% chemical yield. Hydrolysis of 2 with 2 N HCl gave 2-deoxy-2-fluoro-D-glucose (3) in 50% overall chemical yield in a synthesis time of 60 minutes. Preliminary results indicate that this method can be used to synthesize 2-deoxy-2-[^{18}F]fluoro-D-glucose.

Key Words: 2-Deoxy-2-fluoro-D-glucose, xenon difluoride, catalyst, ^{18}F-labeling

INTRODUCTION

For several years, 2-deoxy-2-[^{18}F]fluoro-D-glucose (2-^{18}FDG) has been used for the measurement of regional glucose metabolism in a wide variety of human diseases as well as in the localization and quantitation of normal cortical activity (1-11). As a result, many cyclotron (accelerator)-PETT centers currently synthesize this radiotracer for their own use. However, the low chemical yield from the original 2-^{18}FDG synthesis (12,13) has imposed a limitation on the capabilities for many centers to synthesize sufficient 2-^{18}FDG for their own use. For this reason, the search for new or improved syntheses of 2-^{18}FDG continues.

We recently reported a new improved synthesis of 2-^{18}FDG from ^{18}F-labeled acetyl hypofluorite (14). The radiochemical yield of 2-^{18}FDG using this method is ~ 20%, a factor of two higher than the previous synthesis. The synthesis of 2-^{18}FDG from ^{18}F-labeled fluoride has also been accomplished, although the

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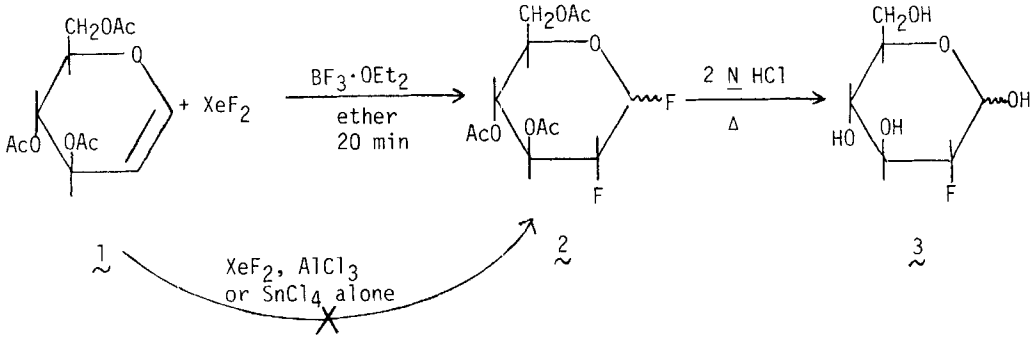
overall radiochemical yield is low (15,16). The synthesis of unlabeled 2-FDG from the reaction of anhydro sugar with KHF_2 (17), nucleophilic substitution at C-2 of deoxyglucose precursor with fluoride (18), electrophilic fluorination with XeF_2 (19) and reaction of glycals with acetyl hypofluorite (20) have also been reported. Although the reaction of 3,4,6-tri-O-acetyl-D-glucal (1) with XeF_2 is reported to provide 2-FDG in high yield, the time scale (e.g. 24 hours) for the sequence was too long to be practical with ^{18}F ($t_{1/2}$ = 110 min). The reports of the synthesis of $[^{18}F]XeF_2$ (21,22) and the application of this reagent for the synthesis of 2-^{18}FDG (23) prompted our reinvestigation of the use of this reagent in the synthesis of 2-^{18}FDG. We report here the synthesis of 2-FDG from the reaction of XeF_2 with 3,4,6-tri-O-acetyl-D-glucal in an overall chemical yield of ~ 50% in a synthesis time of ~ 60 min. This synthesis can be readily applied to the synthesis of 2-^{18}FDG when the methodology has been worked out for producing large quantities of $[^{18}F]XeF_2$.



Scheme 1

EXPERIMENTAL

Materials: 3,4,6-Tri-O-acetyl-D-glucal and xenon difluoride were purchased from Aldrich Chemical Company and PCR Research Chemicals, Inc. respectively and were used without further purification.

Chromatography: Gas-liquid chromatographic analyses (GLC) were carried out either with a Hewlett-Packard 5830A gas chromatograph or with a Perkin-Elmer Sigma 1 gas chromatograph equipped with a thermal conductivity detector. HPLC analyses were carried out with Waters Associates Model 6000 liquid chromatograph equipped with a refractive index detector.

Synthesis of 2-deoxy-2-fluoro-D-glucose from xenon difluoride catalyzed by $BF_3 \cdot OEt_2$: In a typical experiment, a solution of 60.05 mg (0.221 mmol) of 3,4,6-tri-O-acetyl-D-glucal (1) in 10 mL of ethyl ether was added into 45.26 mg (0.267 mmol) of xenon difluoride at room temperature. A solution of 25 µL of $BF_3 \cdot OEt_2$ in 5 mL of benzene was then added. The solution was stirred at room temperature for 20 minutes and then 10 mL of water was added. The organic layer was separated and the aqueous layer was extracted with ethyl ether (3 x 10 mL). The combined organic layer was dried (Na_2SO_4) and evaporated to dryness to give 54.73 mg of residue. The glc of this residue showed only one product which was identified as 2-deoxy-2-fluoro-3,4,6-tri-O-acetyl-D-glucopyranosyl fluoride (2) (or its anomer) by comparison with an authentic sample (12). The absence of 2-deoxy-2-fluoro-3,4,6-tri-O-acetyl-β-D-mannopyranosyl fluoride (12) in the reaction mixture was verified by comparing the retention time of the reaction product with authentic samples.

The residue was dissolved in 10 mL of 2 N HCl and the mixture heated at 130-135°C for 15 min. Activated charcoal was added, the acid was evaporated and 5 mL of aqueous acetonitrile (0.3% H_2O) added and the reaction mixture transferred to a silica gel column (1 x 14 cm). The column was eluted with the same solvent and evaporated to dryness to give 20.23 mg (50.3% chemical yield) of product. The identity of the product as 2-FDG was verified by the formation of the trimethylsilyl derivatives and gas chromatography of the product showed the mass peaks corresponding to the silylated α- and β-anomers of authentic 2-FDG (14). HPLC (14) also confirmed the identity of the product as 2-FDG.

Reaction of 3,4,6-tri-O-acetyl-D-glucal (1) with $[^{18}F]XeF_2$: $[^{18}F]XeF_2$ (4.09 µCi) prepared from $Xe^{19}F_2(p,pn)Xe^{18}F_2$ reaction was dissolved in 5 mL of p-dioxane and then 36.6 mg (0.216 mmol) of carrier XeF_2 added. A solution of 1 (53.4 mg, 0.196 mmol) in 5 mL of p-dioxane was added followed by 25 µL of $BF_3 \cdot OEt_2$ in 5 mL of benzene. The solution was stirred at room temperature for 25 minutes and then 6 mL of water was added. The organic phase was separated and the aqueous phase was extracted with ethyl ether. The combined organic phase was dried (Na_2SO_4) and evaporated to dryness to give 0.61 µCi of product (EOB). The reaction mixture was analyzed by radiogas chromatography and showed the

radioactivity to be congruent with the mass peak corresponding to 2-deoxy-2-fluoro-3,4,6-tri-O-acetyl-D-glucopyranosyl fluoride. The radiochemical yield of 2 was ~ 15% based on [^{18}F]XeF_2.

RESULTS AND DISCUSSION

Xenon difluoride has been shown to be a mild fluorinating agent for the fluorination of alkenes, acetylenes, aromatic and heteroaromatics (24). The mechanism of the fluorination of olefins with xenon difluoride depends on several factors: the structure of the olefin, the catalyst used, solvent polarity, and reaction temperature. Several catalysts such as hydrogen fluoride (25), hydrogen fluoride-pyridine (26), boron trifluoride (27), boron trifluoride etherate (28), trifluoroacetic acid (29), and bromine (30) have been used for the fluorination of olefins with xenon difluoride. The products isolated depend on the catalyst used. Recently, Korytnyk and coworkers report an improved synthesis of 2-deoxy-2-fluorosaccharides by the reactions of glycals with xenon difluoride (19). We have re-investigated this reaction with different catalysts and study its time course.

The reaction of xenon difluoride with 3,4,6-tri-O-acetyl-D-glucal (1) was carried out at room temperature in ethyl ether using different catalysts. When boron trifluoride etherate was used, the reaction was completed in 20 min and gave 2-deoxy-2-fluoro-3,4,6-tri-O-acetyl-D-glucopyranosyl fluoride (2) (or its anomer) as the only product in 70-80% chemical yield. In contrast, when aluminum chloride or stannic chloride was used, it gave complex mixtures with little or none of 2 detected. Treatment of 1 with XeF_2 in ethyl ether at room temperature for 24 hours results in no reaction which is in contrast to the fluorination of various steroid silyl enol ethers with xenon difluoride (31). Hydrolysis of 2 with 2 N HCl gave 3 in ~ 50% chemical yield (based on 1 used) (Scheme 1).

The formation of only 2 (or its anomer) from the reaction of 1 with XeF_2 catalyzed by $BF_3 \cdot OEt_2$ is probably due to the larger size of BF_4^- complex as compared to elemental fluorine resulting in its selective addition to the less hindered side of the double bond as suggested by Korytnyk (19). The selectivity of XeF_2 addition to double bond was also observed in the fluorination of various steroid silyl enol ethers (31).

Using this procedure, the overall chemical yield of 2-FDG is ~ 50% and the synthesis time is ~ 60 minutes. However, in application of this method for the synthesis of 2-^{18}FDG, the maximum radiochemical yield is 50%.

The advantage of using XeF_2 over F_2 in the synthesis of 2-FDG is that only one adduct is formed in the reaction with 1. This is also the case with the recently reported synthesis of 2-FDG and 2-^{18}FDG with acetyl hypofluorite (14,20). The selectivity of these two reagents results in a simplified experimental setup and reduction of the number of steps required to produce the product. However, whereas the acetyl hypofluorite method uses $[^{18}F]F_2$ which is directly available in high yields, the xenon difluoride method still requires the development of a high yield syntheses of $[^{18}F]XeF_2$ before it can be used as a practical alternate route to 2-^{18}FDG. The development of new methods for the production of $[^{18}F]XeF_2$ and use of other catalysts for the reaction are under continued investigation.

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REFERENCES

1. Reivich, M. - Neurosci. Res. Program Bull. 14: 502-504, 1976.
2. Reivich, M., Kuhl, D., Wolf, A. P., et al. - Circ. Res. 44: 127-137, 1979.
3. Reivich, M., Kuhl, D., Wolf, A. P., et al. - Acta Neurol. Scand. 56(Suppl. 64): 190-191, 1977.
4. Reivich, M., Greenberg, J., Alavi, A., et al. - Acta Neurol. Scand. 60(Suppl. 72): 198-199, 1979.
5. Greenberg, J., Reivich, M., Alavi, A., et al. - Science 212: 678-680, 1981.
6. Phelps, M. E., Huang, S.-C., Hoffman, E. J., et al. - Ann. Neurol. 6: 371-388, 1979.
7. Huang, S.-C., Phelps, M. E., Hoffman, E. J. et al. - Am. J. Physiol. 238(Endocrinol. Metab. 1): E-69-E-82, 1980.
8. Brownell, G. L., Ackerman, R. H., Strauss, H. W., et al. - J. Comput. Assist. Tomogr. 4: 473-477, 1980.
9. Ferris, S. H., deLeon, M. J., Wolf, A. P. - Neurobiology of Aging 1: 127-133, 1980.

10. Phelps, M. E., Kuhl, D., and Mazziotta, J. C. - Science 211: 1445-1448, 1981.

11. Alavi, A., Reivich, M., Greenberg, J., et al. - Sem. Nucl. Med. XI: 24-31, 1981.

12. Ido, T., Wan, C.-N., Fowler, J. S. et al. - J. Org. Chem. 42: 2341-2342, 1977.

13. Ido, T., Wan, C.-N., Casella, V. et al. - J. Label. Cmpds. Radiopharm. 14: 175-183, 1978.

14. Shiue, C.-Y., Salvadori, P. A., Wolf, A. P., et al. - J. Nucl. Med. 23: P108, 1982.

15. Levy, S., Livni, E. and Elmaleh, D. R. - J. Nucl. Med. 23: P107, 1982.

16. Elmaleh, D. R., Levy, S., Shiue, C.-Y. et al. - U. S. Patent Pending.

17. Pacak, J., Podesva, J., Tocik, Z., et al. - Coll. Czech. Chem. Comm., 37: 2589-2599, 1972.

18. Tewson, T. J. and Gould, K. L. - J. Nucl. Med. 23: P109, 1982.

19. Korytnyk, W., and Valentekovic-Horvat, S. - Tetrahedron Lett. 21: 1493-1496, 1980.

20. Adam, M. J. - J. C. S. Chem. Comm. 730, 1982.

21. Schrobilgen, G., Firnau, G., Chirakal, R. et al. - J. C. S. Chem. Comm. 198, 1981.

22. Adloff, J. P. and Schleiffer, J. J. - Inorg. Nucl. Chem. Lett. 4: 403-405, 1968.

23. Firnau, G. - First Annual Conjoint Winter Meeting, Society of Nuclear Medicine, New Orleans, Louisiana, February 7, 1981.

24. Filler, R. - Isr. J. Chem. 17: 71-79, 1978.

25. Zupan, M. and Pollak, A. - J. C. S. Chem. Comm. 845, 1973.

26. Gregorcic, A. and Zupan, M. - Coll. Czech. Chem. Comm. 42: 3192, 1977.

27. Stavber, S. and Zupan, M. - J. C. S. Chem. Comm. 969, 1978.

28. Shackelford, S. A., McGuire, R. R. and Pflug, J. L. - Tetrahedron Lett. 363, 1977.

29. Zupan, M. and Pollak, A. - Tetrahedron Lett. 1015, 1974.

30. Stavber, S. and Zupan, M. - J. Fluorine Chem. 10: 271, 1977.

31. Tsushima, T., Kawada, K. and Tsuji, T. - Tetrahedron Lett. 23: 1165-1168, 1982.