Synthesis of 18F-Labelled 2-Fluoro-1,4-quinones Using Acetylhypofluorite

JACOBUS D. M. HERSCHEID,*[1] RINNY WEDZINGA,[1]
WILLEM VERBOOM[2] and GERARD W. M. VISSER[1]

[1]Radio-Nuclide-Centre (RNC), Free University, P.O. Box 7161, 1007 MC Amsterdam, The Netherlands
and [2]Laboratory of Organic Chemistry, University of Twente, P.O. Box 217, 7500 AE Enschede,
The Netherlands

The fluorination of 1,4-benzo- and naphthoquinones using [18F]acetylhypofluorite is described. For compounds with electron-donating substituents fair to good radiochemical yields have been reached.

Introduction

The quinone group is an essential part in a large variety of cytostatic agents, such as the mitomycins[1] and anthracyclines.[2] Since many of these compounds are highly toxic there is a continuous effort towards the synthesis of analogues of these agents, and towards other derivatives with a quinone structure. In this light an easy access to the corresponding radiolabelled compounds to perform biological studies would be helpful. With regard to the choice of radioisotope, the rapid development of positron emission tomography[3] makes the choice of fluorine-18 very attractive.

Recently we have shown that acetylhypofluorite reacts efficiently with activated double bonds, such as found in the pyrimidines, in a regioselective manner.[4 6] This success prompted us to investigate whether [18F]acetylhypofluorite could be applied for the radiofluorination of the quinone moiety. In this paper we report our investigation into the scope and limitations of the reaction of acetylhypofluorite with a variety of 1,4-benzo- and naphthoquinones for the preparation of the corresponding 2-fluoroderivatives.

Materials and Methods

[18F]acetylhypofluorite was prepared by bubbling [18F]F$_2$, obtained by the ^{20}Ne(d, α)^{18}F reaction on ^{20}Ne containing 0.1% F$_2$ (35 μmol),[7] through 15 mL of acetic acid to which 180 μmol of (NH$_4$)$_2$CO$_3$ had been added.[8] Gaseous CH$_3$COOF was produced by passing F$_2$ (1% in N$_2$) through a column of KOAc/HOAc.[9] 1,4-Naphthoquinone (4b) and 2-methyl-1,4-naphthoquinone (4c) were purchased

from Aldrich, the other starting compounds 1a,[10] 1b,[11] 1c,[10] 1d,[12] 1e,[13] 1f,[14] 1g,[15] and 4a,[16] 4d,[17] 4e,[18] 4f,[19] 4h[20] were prepared according to literature methods, whereas 4g was obtained by acylation of 4e with acetic anhydride in the presence of p-toluenesulphonic acid.

Thin layer chromatography was performed on Merck precoated silica gel F-254 plastic plates (thickness 0.2 mm). A mixture of toluene, acetic acid and methanol (v/v/v 8:2:1) was used as eluent for 1 and 3. For the naphthoquinones 4 and 6 a 4:1 v/v mixture of toluene and acetic acid was the eluent of choice. After development spots were visualized by u.v. light and chromatograms were wrapped in adhesive tape, cut into segments of 0.5 cm and counted in a LKB compugamma counter.

HPLC analyses were performed on a silica column (dim: 250 × 4.6 mm, Partisil 10 μm, flow rate 1 mL/min) using a mixture of hexane, ethanol and acetic acid as eluent in a ratio of 79:20:1 v/v for 1 and 3 and a ratio of 89:10:1 v/v for 4 and 6. Peaks were detected by a radioactivity monitor and a u.v. detector (254 nm); fractions of 500 μL were collected and counted for radioactivity.

Proton magnetic resonance spectra were measured on a Bruker WM-250 spectrometer using CDCl$_3$ as solvent. δ-Values are given relative to TMS as internal standard. Reaction products in the naphthoquinone series were identified by GC-mass spectroscopy (type HP 5995A, electron impact ionization, quadrupole mass filter) using a CP SIL 19 CB column (2 min at 343 K and then to 563 K in steps of 10 K min^{-1}).

Radiofluorination of the quinones 1 and 4

To a solution of 20 μmol of 1 or 4 in 1 mL of acetic acid was added 6 μmol of [18F]CH$_3$COOF in 3 mL of

acetic acid. The obtained reaction mixture was ana-
lyzed by TLC and HPLC. The solvent was removed
by evaporation at 300 K; higher temperatures must
be avoided because of sublimation of the quinones.
The residue was allowed to react with
N,N-diisopropylethylamine (dried over KOH) for
5 min, which subsequently was completely evapo-
rated. Acetic acid (2 mL) was added and the solution
was reanalyzed by TLC and HPLC. Radiochemical
yields of **3** and **6** and the characteristics of all
compounds are given in Tables 1 and 2.

Fluorination of the naphthoquinones **4d**, *e, f and g with
gaseous acetylhypofluorite*

Through a solution of 1 mmol of **4** in 25 mL of
acetic acid was bubbled gaseous CH_3COOF. For **4e**
and **4f** the reaction was stopped when HPLC analysis
of the reaction mixture indicated that the formation
of **6** ceased due to its consecutive reaction with
CH_3COOF, whereas for **4d** and **4g**—which initially
gave the intermediate **5**—the reaction was stopped
when all starting material had disappeared. After
removal of the acetic by evaporation, the inter-
mediates **5d** and **5g** were taken up in 2 mL of dry
dioxane and 1 mL of N,N-diisopropylethylamine
(DIEA) was added. After 5–10 min both solvent and
DIEA were removed by evaporation.

The fluorocompounds **6** were purified by column
chromatography on silica (Merck Si 60, 63–40 μm)
using a mixture of toluene and acetic acid as eluent;
ratio 90:10 v/v for **6d**, **6e** and **6g** and 95:5 v/v for **6f**;
flow rate 4 mL/min.

6d: yield 64 mg (31%); ^{1}H-NMR, δ 8.08 (m, 2H),
7.76 (m, 2H), 4.27 (d, 3H, J_{F,OCH_3} = 5.1 Hz); for inter-
mediate **5d** δ 5.47 (d, CHF, $J_{H,F}$ = 47.4 Hz), 3.66
(d, OCH_3, J_{F,OCH_3} = 1.4 Hz), 2.09 (s, OAc).

6e: yield 44 mg (23%); ^{1}H-NMR, δ 8.11 (dd, 1H),
8.04 (dd, 1H), 7.74 (dt, 1H), 7.65 (dt, 1H), 5.03
(s, 2H, NH_2).

6f: yield 39 mg (18%); ^{1}H-NMR, δ 8.11 (dd, 1H),
8.00 (dd, 1H), 7.73 (dt, 1H), 7.61 (dt, 1H), 5.48
(m, 1H, NH), 3.25 (dd, 3H, J_{NH,CH_3} = 5.7 Hz,
J_{F,CH_3} = 5.0 Hz).

6g: yield 63 mg (27%); ^{1}H-MNR, δ 8.15 (m, 2H),
7.78 (m, 2H), 7.46 (s, 1H), 2.31 (s, 3H, NAc); for
intermediate **5g** (*cis*) δ 5.98 (d, CHF, $J_{H,F}$ = 46.0 Hz),
2.31 (s, NAc), 2.14 (s, OAc), **5g** (*trans*) δ 6.30
(d, CHF, $J_{H,F}$ = 48.2 Hz), 2.30 (s, NAc), 2.11
(s, OAc).

Results and Discussion

In analogy with the results obtained in the
fluorination of pyrimidines,[5,6] it was expected that
reaction of benzoquinones with acetylhypofluorite
would give the adduct **2**, which upon elimination of
acetic acid would result in the formation of the
fluoroproducts **3**. Therefore, a variety of benzo-
quinones (Scheme 1) was subjected to the standard
reaction conditions as given in the experimental
section. It was found that fluorination of the mono-
substituted compounds **1a** and **1b** resulted in an
intractable reaction mixture, especially after treat-
ment with the Hünig base diisopropylethylamine

Table 1. Radiochemical yields and characteristics of the
1,4-benzoquinones **1** and **3**

Compound	Yield*	R_t (HPLC)	R_f (TLC)
1c		12.6	0.42
3c	28%	9.3	0.44
1d		16.8	0.40
3d	24%	12.5	0.42
1e		10.3	0.49
3e	27%	11.9	0.40
1f		9.9	0.48
3f	21%	8.3	0.46
1g		20.3	0.39
3g	20%	15.4	0.41

* Maximal theoretical yield based on [^{18}F]F$_2$ is 50%.
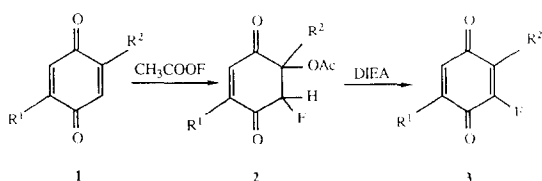
R^1,R^2 = H,OCH_3 (a) ; H, NHAc (b)

R^1 = R^2 = OCH_3 (c) ; NHCH$_3$ (d) ; NHAc (e) ; c NC$_5$H$_{10}$ (f) ; c - NC$_2$H$_4$ (g)

Scheme 1

Table 2. Radiochemical yields and characteristics of the 1,4-naphthoquinones **4** and **6**

Compound	Yield*	R_t (HPLC)	R_f (TLC)	R_t (GCMS)	M$^+$ (% abundancy)
4c		5.2	0.53	12.82	172 (100)
6c	8%	5.1	0.54	12.90	190 (80)
4d		8.6	0.44	16.66	188 (59)
6d	37%	7.1	0.49	15.20	206 (100)
4e		11.0	0.26	18.22	173 (100)
6e	23%	11.5	0.35	17.14	191 (93)
4f		12.0	0.34	18.32	187 (100)
6f	19%	9.3	0.51	17.82	205 (100)
4g		11.5	0.35	19.72	215 (84)
6g	28%	14.8	0.30	19.05	233 (100)
4h		10.2	0.43	22.76	227 (100)
6h	9%	10.0	0.45	21.88	245 (100)

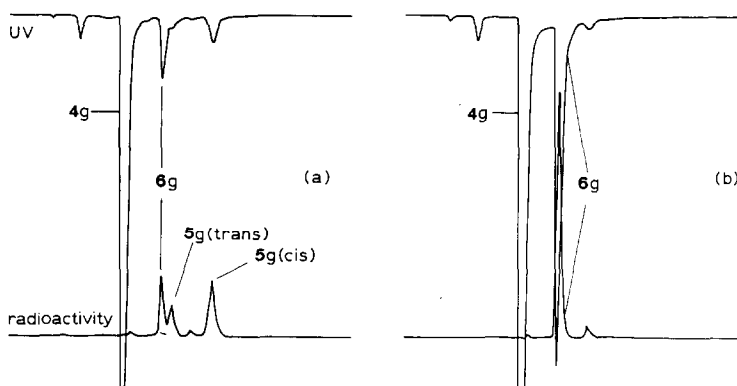* Maximal theoretical yield based on [^{18}F]F$_2$ is 50%.

Fig. 1. HPLC analyses of the reaction mixture of **4g** with CH₃COOF (a) before and (b) after treatment with DIEA.

(DIEA). A likely explanation is that these mono-substituted compounds and their reaction products act as good Michael acceptors, thus resulting in the formation of many byproducts. In line with this explanation, the reaction of [¹⁸F]acetylhypofluorite with the disubstituted quinones **1c–g** gave one major radioactive product. This product was formed either directly (**d**, **f** and **g**) or just after treatment with DIEA (**c** and **e**).

The observed difference is caused by the presence of a free lone-pair at the nitrogen atom in **2d**, **2f** and **2g**, which renders these half-aminal instable in contrast with **2c** and **2e**. Although TLC and HPLC results (Table 1) clearly indicated the formation of **3**, an unambiguous identification was not possible, since all benzoquinones appeared to be destroyed under our GCMS-conditions.

Since it was observed that most naphthoquinones were stable against the GCMS-conditions, it was decided to use this class of compounds for a further study of the reaction of acetylhypofluorite with 1,4-quinones. In the naphthoquinone series (Scheme 2) it was found that the presence of an electron-donating group attached to the double bond is a prerequisite for the reaction to occur. Compounds **4a** and **4b** failed to give any fluorinated product at all, whereas the yield of **6c** was only 6% (Table 2). With the exception of **6h** all other fluorinated naphthoquinones were obtained in reasonable to high radiochemical yields. These findings are in accordance with our earlier proposed SET-mechanism,[21,22] since it is known that electron donating substituents

lower the first ionisation potential of quinones which can even result in the formation of stable radical cations.[23]

As was found with the benzoquinones, those compounds having a free lone-pair at nitrogen in the half-aminal intermediate (**5e**, **f** and **h**) gave the fluoroproduct **6** directly. The intermediary of **5d** and **5g** was established both by HPLC-analysis (Fig. 1) as by ¹H-NMR spectroscopy of the crude reaction mixture. The observed coupling constants of approximately 47 Hz confirm that the fluorine and hydrogen atom are in a geminal position. Whereas for **5d** only one isomer was observed, **5g** consisted of two diastereomers in a ratio of about 2 to 1. In line with earlier results it is expected that the cis-isomers are formed predominantly.[4,6] Although **5d** and **5g** were relatively stable compounds, their formation was always accompanied by a substantial amount of **6**. This direct formation of **6d** and **6g** can be explained by the abstraction of a hydrogen atom at C-2 by the acetoxy radical (vide infra) as has been found in the fluorination of uracils.[5,24] Based on the observation that some of the naphthoquinones (**4d**, **e**, **f** and **g**) gave relatively high radiochemical yields, it seemed worthwhile investigating whether acetylhypofluorite is a useful agent for the preparation of the fluoronaphthoquinones on a larger scale. To avoid high concentrations of acetylhypofluorite, which might lead to explosions, gaseous acetylhypofluorite was used for this purpose. However, under the applied conditions the yields of **6** were much lower and the amounts of byproducts much higher than has been observed in the radiofluorinations where a large excess of starting material was used. Some of these byproducts could be identified by GCMS analysis of the crude reaction mixtures. Those of the reactions of **4d** with acetylhypofluorite are depicted in Fig. 2. Compound **7** is presumably formed by a trans-addition of acetylhypofluorite followed by elimination of methanol. The partial decomposition of an intermediate acetoxy radical before recombination[21,22] would explain the formation of **8**;
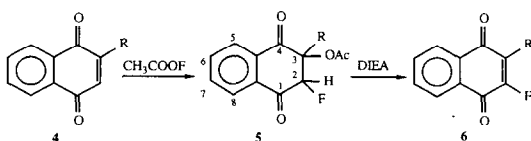
· R = Cl (a) ; H (b) ; CH₃ (c) ; OCH₃ (d) ; NH₂ (e) ; NHCH₃ (f) ; NHAc (g) ; c · NC₅H₁₀ (h)
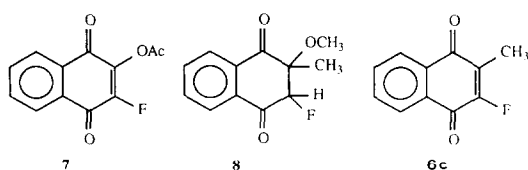
Scheme 2

Fig. 2. Identified byproducts from the reaction of **4d** with gaseous CH_3COOF.

6c is then formed from *trans* **8** through elimination of methanol. This again indicates that the mechanism by which acetylhypofluorite reacts is not just electrophilic.

In conclusion, it has been found that acetylhypofluorite is a good agent for the fluorination of 1,4-quinones when applied on a μmol scale i.e. for the preparation of the fluorine-18 labelled ones. However, for the synthesis of 2-fluoro-1,4-quinones on a larger scale it seems less ideal. Work is in progress to evaluate whether the newly developed milder agents N-fluoropyridinium triflates[25] can be applied for this purpose.

References

1. (a) Remers W. A. *The Chemistry of Antitumor Antibiotics* Vol. 1, chap. 5, p. 221. (John Wiley, New York, 1979); (b) Carter S. K. and Crooke S. T. *Mitomycin C—Current Status and New Developments*. (Academic Press, New York, 1979); (c) Ogawa M., Rosenczweig M. and Staquet M. J. *Mitomycin C—Current Impact on Cancer Chemotherapy* (Excerpta Medica, Princeton, 1982).
2. (a) Arcamone F. *Doxorubicin Anticancer Antibiotics* (Academic Press, New York, 1981); (b) Arcamone F. *Med. Res. Rev.* **4**, 153 (1984).
3. Wagner H. N. Jr. *Diagnostic Imaging* 82 (1986).
4. Van Rijn C. J. S., Herscheid J. D. M., Visser G. W. M. and Hoekstra A. *Int. J. Appl. Radiat. Isot.* **36**, 111 (1985).
5. Visser G. W. M., Boele S., Halteren B. W. van, Knops G. H. J. N., Herscheid J. D. M., Brinkman G. A. and Hoekstra A. *J. Org. Chem.* **51**, 1466 (1986).
6. Visser G. W. M., Noordhuis P., Zwaagstra O., Herscheid J. D. M. and Hoekstra A. *Appl. Radiat. Isot.* **37**, 1074 (1986).
7. Casella V., Ido T., Wolf A. P., Fowler J. S., MacGregor R. R. and Ruth T. J. *J. Nucl. Med.* **21**, 750 (1980).
8. Shiue C. Y., Salvadori P. A., Wolf A. P., Fowler J. S. and MacGregor R. R. *J. Nucl. Med.* **23**, 899 (1982).
9. Jewitt D. M., Potochi J. F. and Ehrenkaufer R. E. *J. Fluorine Chem.* **24**, 477 (1984).
10. Teuber H. J. and Rau W. *Chem. Ber.* **86**, 1036 (1953).
11. Teuber H. J. and Gosauer O. *Chem. Ber.* **98**, 2939 (1965).
12. Garreau Y. *Bull. Soc. Chim. Fr.* 501 (1950).
13. Fr. patent 1 345 524 (1963); J. R. Geigy A.-G. *Chem. Abstr.* **60**, 11951 (1964).
14. Marxer A. *Helv. Chim. Acta* **38**, 1473 (1955).
15. British patent 762 723 (1956); Farb. Fab. Bayer A.-G. *Chem. Abstr.* **51**, 12153h (1957).
16. Fieser L. F. *J. Am. Chem. Soc.* **70**, 3165 (1948).
17. Otsuki T. *Bull. Chem. Soc. Jpn.* **47**, 3089 (1974).
18. Fieser L. F. and Hartwell J. L. *J. Am. Chem. Soc.* **57**, 1482 (1935).
19. Belg. patent 614136 (1962); U.S. Rubber Co. *Chem. Abstr.* **57**, 15031 (1962).
20. Falling S. N. and Rapoport H. *J. Org. Chem.* **45**, 1260 (1980).
21. Visser G. W. M., Bakker C. N. M., Halteren B. W. van, Herscheid J. D. M., Brinkman G. A. and Hoekstra A. *Recl. Trav. Chim. Pays-Bas* **105**, 214 (1986).
22. Visser G. W. M., Bakker C. N. M., Halteren B. W. van, Herscheid J. D. M., Brinkman G. A. and Hoekstra A. *J. Org. Chem.* **51**, 1886 (1986).
23. Bock H., Hänel P., Kaim W. and Lechner-Knoblauch U. *Tetrahedron Lett.* **26**, 5115 (1985).
24. Visser G. W. M., Herder R. E., Kanter J. J. de and Herscheid J. D. M. *J. Chem. Soc. Perkin Trans 1* In press (1988).
25. Umemoto T. and Tomita K. *Tetrahedron Lett.* **27**, 3271 (1986).