Synthesis of $^{18}$F-Labelled 2-Fluoro-1,4-quinones Using Acetylhypofluorite

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The fluorination of 1,4-benzo- and naphthoquinones using $[^{18}$F]$^\text{acetylhypofluorite}$ 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 and anthracyclines. 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 radio-labelled compounds to perform biological studies would be helpful. With regard to the choice of radioisotope, the rapid development of positron emission tomography makes the choice of fluorine-$^{18}$F very attractive.

Recently we have shown that acetylhypofluorite reacts efficiently with activated double bonds, such as found in the pyrimidines, in a regioselective manner. This success prompted us to investigate whether $[^{18}$F]$^\text{acetylhypofluorite}$ 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 fluoro derivatives.

Materials and Methods

$[^{18}$F]$^\text{acetylhypofluorite}$ was prepared by bubbling $[^{18}$F]$^\text{F}_2$, obtained by the $^\text{2}$Ne$(d, \alpha)^{19}$F reaction on $^\text{2}$Ne containing 0.1% F$_2$ (35 pmol), through 15 mL of acetic acid to which 180 pmol of (NH$_2$)$_2$CO$_2$ had been added. Gaseous CH$_2$COOF was produced by passing F$_2$ (1% in N$_2$) through a column of KOAc/HOAc. 1,4-Naphthoquinone (4b) and 2-methyl-1,4-naphthoquinone (4c) were purchased from Aldrich, the other starting compounds 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 3a, 3b, 3c, 3d, 3e, 3f, 3g were prepared according to literature methods, whereas 4g was obtained by acylation of 4e with acetic anhydride in the presence of $p$-toluenesulfonic 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 x 4.6 mm, Partisol 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. $\delta$-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 $[^{18}$F]$^\text{CH}_2$COOF in 3 mL of...
acetic acid. The obtained reaction mixture was analyzed 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 evaporated. Acetic acid (2 mL) was added and the solution was reanalyzed by 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$_2$COOF. 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$_2$COOF, 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 intermediates 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.

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield*</th>
<th>$R_f$ (HPLC)</th>
<th>$R_f$ (TLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>26%</td>
<td>12.6</td>
<td>0.42</td>
</tr>
<tr>
<td>1e</td>
<td>24%</td>
<td>16.8</td>
<td>0.44</td>
</tr>
<tr>
<td>1d</td>
<td>24%</td>
<td>12.5</td>
<td>0.42</td>
</tr>
<tr>
<td>1f</td>
<td>21%</td>
<td>10.3</td>
<td>0.49</td>
</tr>
<tr>
<td>1g</td>
<td>21%</td>
<td>11.9</td>
<td>0.40</td>
</tr>
<tr>
<td>1h</td>
<td>21%</td>
<td>9.9</td>
<td>0.48</td>
</tr>
<tr>
<td>1i</td>
<td>21%</td>
<td>8.3</td>
<td>0.46</td>
</tr>
<tr>
<td>1j</td>
<td>20%</td>
<td>20.3</td>
<td>0.39</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield*</th>
<th>$R_f$ (HPLC)</th>
<th>$R_f$ (TLC)</th>
<th>$R_f$ (GCMS)</th>
<th>$M^+$ (% abundance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c</td>
<td>8%</td>
<td>5.2</td>
<td>0.53</td>
<td>12.82</td>
<td>172 (100)</td>
</tr>
<tr>
<td>4d</td>
<td>8%</td>
<td>5.1</td>
<td>0.54</td>
<td>12.90</td>
<td>190 (80)</td>
</tr>
<tr>
<td>4e</td>
<td>8%</td>
<td>8.6</td>
<td>0.44</td>
<td>16.66</td>
<td>188 (59)</td>
</tr>
<tr>
<td>4f</td>
<td>37%</td>
<td>7.1</td>
<td>0.49</td>
<td>15.20</td>
<td>206 (100)</td>
</tr>
<tr>
<td>4g</td>
<td>23%</td>
<td>11.0</td>
<td>0.26</td>
<td>18.22</td>
<td>173 (100)</td>
</tr>
<tr>
<td>4h</td>
<td>19%</td>
<td>11.5</td>
<td>0.35</td>
<td>17.14</td>
<td>191 (93)</td>
</tr>
<tr>
<td>4i</td>
<td>19%</td>
<td>12.0</td>
<td>0.34</td>
<td>18.32</td>
<td>207 (100)</td>
</tr>
<tr>
<td>4j</td>
<td>19%</td>
<td>9.3</td>
<td>0.51</td>
<td>17.82</td>
<td>205 (100)</td>
</tr>
<tr>
<td>4k</td>
<td>28%</td>
<td>11.5</td>
<td>0.35</td>
<td>19.72</td>
<td>215 (64)</td>
</tr>
<tr>
<td>4l</td>
<td>28%</td>
<td>14.8</td>
<td>0.30</td>
<td>19.05</td>
<td>233 (100)</td>
</tr>
<tr>
<td>4m</td>
<td>9%</td>
<td>10.2</td>
<td>0.43</td>
<td>22.76</td>
<td>227 (100)</td>
</tr>
</tbody>
</table>

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

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Results and Discussion

In analogy with the results obtained in the fluorination of pyrimidines,\(^{18}\) 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 benzoquinones (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 treatment with the Hüning base diisopropylethylamine.
(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 [$^{18}$F]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-aminals unstable 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, 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. 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 $^1$H-NMR spectroscopy of the crude reaction mixture. The observed coupling constants of approximately 47 Hz confirm that the fluorine and hydrogen atoms 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. 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. 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 would explain the formation of 8.
Fig. 2. Identified byproducts from the reaction of 4d with gaseous CH$_2$COOF.

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.

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References