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Author(s)
Akiyama, Yuriko; Fukuhara, Tsuyoshi; Hara, Shoji

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Regioselective Synthesis of Fluorohydrines via $S_N2$-Type Ring-Opening of Epoxides with Bu$_4$N-HF$_2$-KHF$_2$

Yuriko Akiyama, Tsuyoshi Fukuhara, Shoji Hara*

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
Fax: +81-11-706-6556; E-mail: hara@org-mc.eng.hokudai.ac.jp

Abstract: We found that the ring-opening fluorination of terminal epoxides using TBABF-KHF$_2$ proceeds with high selectivity through the $S_N2$ mechanism. As TBABF-KHF$_2$ is easily obtainable, is stable, and can be used in glassware, it can be a useful reagent for 1-fluoro-2-alkanol synthesis from the terminal epoxides.

Key words: epoxides, fluorohydrine, regioselectivity, ring-opening, tetrabutylammonium bifluoride (TBABF)-KHF$_2$

Ring-opening reaction of epoxides with a fluoride ion has been widely used to prepare organofluorine compounds. Especially, regioselective fluorination of terminal epoxides has attracted much attention because optically active fluorohydrines, expected as building blocks for liquid crystal materials, can be prepared from easily accessible, optically active terminal epoxides by that method. Though many reagents for regioselective ring-opening fluorination of terminal epoxides have been reported, only a few of them successfully obtained good regioselectivity for 1-fluoro-2-alkanols (Equation 1).

\[
\text{Equation 1}
\]

Schlosser et al. attained high regioselectivity (> 90%) for 2 by $i$-Pr$_2$NEt-HF, and Yoshioka et al. succeeded by using Pb$_4$F(HF)$_n$. However, they each showed only one example and the generality of their methods was not confirmed. Furthermore, a drawback of these methods is that the reagents are not easily available. We wish to report here that high regioselectivity (> 90%) for 2 was realized by Bu$_4$N’HF$_2$(TBABF)-KHF$_2$, prepared from commercially available Bu$_4$NF (TBAF), aq HF, and KHF$_2$. The application of TBAF to the reaction with 1-octene oxide (1a) resulted in poor selectivity and chemical yield as shown in Table 1, and a
significant amount of Bu$_3$N was found after the reaction at 100 °C. As the fluoride ion of
the TBAF is highly basic, Hofmann-type elimination took place under the reaction conditions
and the TBAF decomposed to Bu$_3$N, butene, and HF.$^5$ TBAF-5H$_2$O, reported to be less basic
than TBAF, also gave a poor result.$^6$ On the other hand, TBABF reacted with 1a at 100 °C
to give 2a in 78% yield with good regioselectivity (90%).$^7$ However, application of longer
reaction time or higher reaction temperature (120 °C) could not improve the yield, and the
formation of Bu$_3$N was observed after the reaction. Though TBABF is stable at below
140 °C, after the reaction with epoxides, it changes to the TBAF. The addition of KHF$_2$ was
found to be effective not only to suppress the formation of Bu$_3$N but also to improve the yield.
In the reaction of 1a with 3 equivalents of TBABF and 0.3 equivalents of KHF$_2$ at 120 °C, 2a
was obtained in 92% yield and with good selectivity (91%).$^8$ Though TBAF-2HF (TBATF)
also showed high reactivity in the reaction with 1a, the regioselectivity was less satisfactory.

Table 1  Fluorination of 1a with Various Reagents

<table>
<thead>
<tr>
<th>Fluorination reagent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBAF$^c$</td>
<td>rt</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>TBAF</td>
<td>100</td>
<td>18</td>
<td>37 (84 : 16)</td>
</tr>
<tr>
<td>TBAF-5H$_2$O</td>
<td>100</td>
<td>18</td>
<td>36 (72 : 28)</td>
</tr>
<tr>
<td>TBABF</td>
<td>100</td>
<td>18</td>
<td>78 (90 : 10)</td>
</tr>
<tr>
<td>TBABF</td>
<td>120</td>
<td>4</td>
<td>73 (90 : 10)</td>
</tr>
<tr>
<td>TBATF</td>
<td>120</td>
<td>4</td>
<td>97 (78 : 22)</td>
</tr>
<tr>
<td>TBABF-KHF$_2$d</td>
<td>120</td>
<td>4</td>
<td>92 (91 : 9)</td>
</tr>
</tbody>
</table>

$^a$ If otherwise not mentioned, fluorination reagent (3 mmol),
1a (1 mmol) and heptane (0.1 mL) were used.
$^b$ $^{19}$F NMR yield using FCH$_2$CH$_2$OH as internal standard. In
parentheses, ratio of 2a : 3a obtained by $^{19}$FNMR.
$^c$ 3 mL of 1 M THF solution of TBAF was used.
$^d$ TBABF(3 mmol), KHF$_2$ (0.3 mmol) and heptane (0.1 mL)
were used.

The generality of our method for the selective formation of the terminal fluorides 2 was
shown in the reaction with various terminal epoxides (Table 2). Even in the reaction with
styrene oxide (1b), which is apt to give $S_N1$ product 3b,$^9a,10$ $S_N2$ product 2b was obtained
with good selectivity. Sattler and Haufe reported that in the reaction of Et$_3$N-nHF reagents
with ethyl 10,11-epoxy undecanoate (1c), the isolation of the corresponding fluoroxydrine
products from the amine mixtures was difficult. In the reaction of 1c with TBABF-KHF₂, the fluorohydrine 2c was obtained in good yield and with high selectivity. From 1-oxaspiro[2,5]octane derivative 1e and glycidol derivative 1f, 2e and 2f were exclusively obtained.

Table 2  Fluorination of Various Epoxides with TBABF-KHF₂

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (h)</th>
<th>Yield of 2 (%)b</th>
<th>2 : 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph 1b</td>
<td>2</td>
<td>86 (68)</td>
<td>90 : 10</td>
</tr>
<tr>
<td>EtOOC(CH₂)₈ 1c</td>
<td>6</td>
<td>86 (65)</td>
<td>90 : 10</td>
</tr>
<tr>
<td>1d</td>
<td>4</td>
<td>71</td>
<td>—</td>
</tr>
<tr>
<td>1Bu 1e</td>
<td>4</td>
<td>75 (74)</td>
<td>&gt;99 : &lt;1</td>
</tr>
<tr>
<td>1f</td>
<td>4</td>
<td>92 (72)</td>
<td>98 : 2</td>
</tr>
</tbody>
</table>

| a) 3 equivalents of TBABF, 0.3 equivalents of KHF₂, and 0.1 mL of heptane were used to 1 (1 mmol).  
| b) ¹⁹F NMR yield using FCH₂CH₂OH as an internal standard, in parentheses, isolated yield based on 1.  
| c) Determined by ¹⁹F NMR. |

TBABF-KHF₂ is applicable to the synthesis of optically active fluorohydrines, and (S)-1-fluoro-2-phenyl-2-ethanol of 98%ee was obtained in 90% yield from commercially available (S)-(−)-styrene oxide (98%ee) as shown in Scheme 1. Interestingly, the minor product, 2-phenyl-2-fluoroethanol (3b), also kept the optical purity of the starting epoxide. Therefore, both 2b and 3b were formed via the S₂N₂ mechanism without racemization.
Scheme 1

References


(8) The generated TBAF must be converted to the stable TBABF again by KHF₂ before the decomposition to Bu₃N.⁹ As KHF₂ is slightly soluble in the reaction mixture, further addition of KHF₂ was not effective.


(11) Enantiomeric excess values of (S)-2b and (R)-3b were determined from ¹⁹F NMR after
conversion to MTPA esters.

(12) The representative procedure for 2a is as follows: To a 1 M THF solution of TBAF (30 mL, 30 mmol) in a glass vessel was added 46% aq HF (1.3 g, 30 mmol) and the volatile part was removed by evaporator to give a crude TBABF. The crude TBABF, containing a little water, is storable in a glass bottle. The crude TBABF (845 mg, 3 mmol) and KHF₂ (24 mg, 0.3 mmol) were put in a glass vessel and water was completely removed (for 15 min at 100 °C and 0.55 mmHg). After cooling to room temperature, heptane (0.1 mL) and 1a (1 mmol) were added. The mixture was kept at 120 °C for 4 h and then cooled to room temperature again. To the reaction mixture, 2 mL of water was added and the mixture was extracted with ether (2 mL x 3). NMR yield and the product ratio were determined from ¹⁹F NMR using FCH₂CH₂OH as an internal standard. Isolation was carried out by column chromatography (silica gel/hexane-ether) after concentration. 2a: IR (film) 3390, 2930, 1460 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.50-4.20 (m, 2H), 3.89-3.86 (m, 1H), 2.00 (s, 1H), 1.48-1.43 (m, 3H), 1.33-1.28 (m, 7H), 0.89 (t, 3H, J = 7.0 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -228.81 (dt, J = 18.3, 47.7 Hz, 1F); 3a: IR (film) 3365, 2930, 1466 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.58 (dm, J = 50.3 Hz, 1H), 3.79-3.61 (m, 2H), 1.88 (t, J = 6.3 Hz, 1H), 1.75-1.30 (m, 12H), 0.89 (t, 3H, J = 6.8 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -190.03 -190.42 (m, 1F).


(15) Complete removal of water gave pure TBABF as a highly viscous liquid which is difficult to handle. Therefore, it is better to store the crude TBABF and to remove the water completely just before use. TBABF is commercially available and TBABF obtained from Tokyo Kasei Kogyo Co., Ltd. showed the same reactivity.

(16) Heptane was used to wash the substrates attached on the wall of the vessel during the reaction, and in a larger-scale experiment, the solvent is not necessary.

(17) Spectra data of TBABF thus prepared coincided with the reported ones; ¹⁹F NMR (CD₂Cl₂, -80 °C) δ -151.5 (d, J₉F = 123.0 Hz), lit. ¹⁹F NMR (CD₂Cl₂, -80 °C) δ -147.5 (d, J₉F = 123.3 Hz).
