Additions of Acetonitrile and Chloroform to Aromatic Aldehydes in the Presence of Tetrabutylammonium Fluoride

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Addition reactions of acetonitrile to aldehydes afford \( \beta \)-hydroxynitriles which can be converted into amino, carboxyl or other functional groups in organic chemistry. Cyano- methylation has been performed by deprotonation of a nitrile compound followed by addition to an aldehyde or a ketone. Depending on the reaction conditions, \( \alpha,\beta \)-unsaturated nitriles are given as in aldol-type condensations. There have been some reports describing various methods of cyanomethylation. Addition reactions of a trichloromethyl group to aldehydes give trichloromethyl carbinols which can be converted into \( \alpha \)-amino, \( \alpha \)-hydroxy and \( \alpha \)-thio acids. The reaction can be carried out by base-mediated addition of the trichloromethyl group to an aldehyde or ketone as the same manner as in cyanomethylation. Reagents of trichloromethylation are made of a \( \text{CCl}_3^- \) source such as chloroform, tetrachloro- methane and (trimethylsilyl)trichloromethane and bases such as \( n \)-butyl lithium, potassium \( \text{t-BuO}^- \), potassium hydroxide, and DBU. When strong bases are used, a carbene could be generated in some cases.

Tetrabutylammonium fluoride (TBAF) is a typical desilylation agent for breaking oxygen-silicon or carbon-silicon bonds and plays a role as a base or a nucleophilic fluorination reagent. Recently, we have found an equivalent of TBAF can oxidize benzaldehyde to benzoic acid. During the studies on solvent effects in the oxidations of aromatic aldehydes with TBAF, we observed cyanomethylation and trichloromethylation with certain aldehydes. In this paper, we described cyanomethylation and trichloromethylation, as well as competition with oxidation.

Results and Discussion

Since the oxidation of \( p \)-nitrobenzaldehyde with TBAF into \( p \)-nitrobenzoic acid was faster in acetonitrile than in other solvents, the reaction in CH\(_3\)CN was examined with other benzaldehydes. In variation of the electronic effect of the substituents in para position of benzaldehyde, five different benzaldehydes were employed. As shown in Table 1, the oxidation reaction competed with the cyanomethylation. The reaction mechanism of oxidation has been studied in our laboratory, but it was not clear until now. Deprotonation of acetonitrile by TBAF generated cyanomethyl anion which was added into a carbonyl group to give a \( \beta \)-hydroxynitrile (Scheme 1).

In the case of the \( p \)-nitro derivative, oxidation took place to give the corresponding acid and no cyanomethylation was observed (Table 1, entries 1 and 2). As the oxidation proceeded, the basicity of TBAF decreased. When excess of TBAF was used in the case of \( p \)-CF\(_3\), the starting material

### Table 1. Cyanomethylation of aromatic aldehydes\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>Y</th>
<th>TBAF (equiv)</th>
<th>CH(_3)CN (equiv)</th>
<th>time (h)</th>
<th>yield(^b)</th>
<th>SM(^c) alcohol</th>
<th>Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO(_2)</td>
<td>1.2</td>
<td>3</td>
<td>12</td>
<td>17</td>
<td>–</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>NO(_2)</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>CF(_3)</td>
<td>1.2</td>
<td>3</td>
<td>12</td>
<td>42</td>
<td>–</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>CF(_3)</td>
<td>3</td>
<td>3</td>
<td>12</td>
<td>–</td>
<td>63</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>1.2</td>
<td>3</td>
<td>12</td>
<td>–</td>
<td>99(87)</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>3</td>
<td>1.2</td>
<td>3</td>
<td>–</td>
<td>99</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>1.2</td>
<td>3</td>
<td>12</td>
<td>10</td>
<td>90</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>3</td>
<td>1.2</td>
<td>3</td>
<td>–</td>
<td>99</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>tBu</td>
<td>1.2</td>
<td>3</td>
<td>12</td>
<td>24</td>
<td>76</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>tBu</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>–</td>
<td>99(93)</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\)The reaction took place with 1.0 M TBAF in THF at 25 °C. \(^b\)The relative yields were calculated by integrations of NMR data and the isolated one was in parenthesis. \(^c\)SM means the starting materials, and the same notation will be applied in the following tables.

Scheme 1. Addition of acetonitrile to aromatic aldehydes (Cyanomethylation).

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When excess of acetonitrile was used, the rate of cyanomethylation was much faster than that of oxidation (entries 5-10).

As shown in Table 2, the reaction of p-trifluoromethylbenzaldehyde gave a mixture of p-trifluoromethylbenzoic acid, the oxidation product and 3-hydroxy-3-(p-trifluoromethyl)phenylpropanenitrile, the cyanomethylated one. When excess of acetonitrile was used, the rate of cyanomethylation was faster than that of oxidation.

In conclusion, cyanomethylation proceeded faster, as the reaction temperature increased, cyanomethylation also took place more readily.

In conclusion, cyanomethylation proceeded faster, as the electron withdrawing effect increased, unless the oxidation took place. In the case of p-nitro, only oxidation took place. The competition mainly depended upon the electronic effect of the substituents.

When the 1H nmr spectrum of p-nitrobenzaldehyde was recorded in CDCl3 in the presence of TBAF, the characteristic peak of a benzyl alcohol was detected. The trichloromethylation was incorporated in the reaction mixtures, when the oxidation reaction of benzaldehydes with TBAF was carried out in chloroform as a solvent. As shown in Table 3, the trichloromethylation took place without competition of the oxidation. As the electronic withdrawing effect of the substituents increased, the rate of reaction was faster (entries 1, 3, 5, 8, 11). When the reaction temperature went up, the rate also became faster a little (entries 7, 10, 13). The mechanism was the same as that of the cyanomethylation. Deprotonation of CHCl3 by TBAF and the resulting CCl3 anion was added into the benzaldehydes to give α-trichloromethylbenzyl alcohols. In the cases of p-NO2 and p-CF3, one equivalent of TBAF was enough proceeding the reaction in a short period of time.

To complete the trichloromethylation of other benzaldehydes, various reaction conditions were tested. Higher temperature was needed for p-chlorobenzaldehyde, but the amount of chloroform was more crucial, as shown in Table 4. When more than 1 equivalent of TBAF was used, excess of chloroform was enough ending the reaction. The reaction more depended upon the amount of chloroform than that of TBAF (entries 2 and 3).

In the case of hexanal, as an aliphatic aldehyde bearing α-protons, the reaction in acetonitrile gave a mixture of compounds, presumably because the cyanomethylation and extensive aldo-type condensations occurred, while the reaction in chloroform gave mainly 1,1,1-trichloro-2-heptanol, the trichloromethylated compound at lower temperature. Additions of a cyanomethyl group to ketones bearing α-protons gave complex mixtures like aldehydes, while the trichloromethylation did not take place.

Conclusion

When the reaction of para substituted benzaldehyde with acetonitrile took place in the presence of TBAF, cyanomethylation competed with oxidation depending upon the electronic effect of the substituent, while the reaction in
chloroform gave only chloromethylated products. Generally, cyanomethylation and trichloromethylation proceeded faster, as the electron withdrawing effect increased, unless the oxidation took place. To complete the reaction, excess of TBADF was needed in case of cyanomethylation, while excess of chloroform was needed in trichloromethylation.

**Experimental Section**

All reactions were performed in vials. Compounds such as tetrahydroammonium fluoride (1.0 M solution in tetrahydrofuran), p-nitrobenzaldehyde, p-trifluoromethylbenzaldehyde, p-chlorobenzaldehyde, benzaldehyde, and p-tert-butylbenzaldehyde were purchased from Aldrich. Acetonitrile and Acetonitrile (0.032 mL, 0.61 mmol) and 1.0 M tetrabutylammonium fluoride in THF (0.24 mL, 2.71 (d, 2H), 1.26 (s, 9H); 3f

1.0 M tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) was needed in case of cyanomethylation, while oxidation took place. To complete the reaction, excess of chloroform gave chloromethylated products. Generally, cyanomethylation and trichloromethylation proceeded faster, as the electron withdrawing effect increased, unless the oxidation took place. To complete the reaction, excess of TBADF was needed in case of cyanomethylation, while excess of chloroform was needed in trichloromethylation.

**Typical procedure for the cyanomethylation of p-chlorobenzaldehyde.** Acetonitrile (0.032 mL, 0.61 mmol) and 1.0 M tetrahydroammonium fluoride in THF (0.24 mL, 0.24 mmol) were placed in a 5 mL vial. After stirring for 0.5 h, p-chlorobenzaldehyde (28.1 mg, 0.20 mmol) was added to the reaction mixture which was stirred at 25°C for 12 h. The reaction mixture was poured into water and extracted three times with ether. The organic layer was dried with anhydrous magnesium sulfate, and then evaporated under reduced pressure to give 3-(4-chlorophenyl)-3-hydroxypropionitrile as a crude product. The product was purified by column chromatography (ethyl acetate : hexane = 2 : 8). The NMR data have been reported.

**3-(4-Trifluoromethylphenyl)-3-hydroxypropionitrile.** 1H NMR (CDCl3, 200 MHz) δ 7.67 (d, 2H), 7.59 (d, 2H), 5.13 (t, 1H), 2.73 (d, 2H); 13C NMR (CDCl3, 100 MHz) δ 144.8, 130.9 (q, Jc,F = 38.3 Hz), 125.9, 116.9, 69.3, 28.0. Anal. Calcd for C13H14F3NO: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.67; N, 6.36; H, 3.90.

**3-Phenyl-3-hydroxypropionitrile.** NMR data have been reported.**

**3-(4-tert-Butylphenyl)-3-hydroxypropionitrile.** 1H NMR (CDCl3, 200 MHz) δ 7.38-7.19 (m, 4H), 4.96 (t, 1H), 2.71 (d, 2H), 1.26 (s, 9H); 13C NMR (CDCl3, 100 MHz) δ 152.0, 318.0, 125.9, 125.3, 117.3, 70.0, 34.6, 31.3, 27.8. Anal. Calcd for C13H17NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.74; H, 8.67; N, 6.67.

**General procedure for the trichloromethylation.** The procedure outlined above was followed using chloroform instead of acetonitrile.

**2.2.2-Trichloro-1-(4-nitrophenyl)ethanol.** NMR data have been reported.

5. (c) Reeve, W. Synthesis 1971, 131.
11. A paper on the oxidation will be in submission.